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THE DUMPING SYNDROME

I. FACTORS RESPONSIBLE FOR THE SYMPTOMS

BY

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The dumping syndrome is one cause of an unsatisfactory result after the operation of subtotal gastrectomy. Symptoms come on towards the end of or shortly after meals, the main features being feelings of abdominal distension, often accompanied by borborygmi, and of extreme exhaustion with faintness, dizziness, sweating, and palpitations. These symptoms, which are exacerbated by standing and relieved by recumbency, last for some 30–45 minutes. A severe attack may culminate in the passage of a loose motion. The onset or fear of symptoms restricts the size of meals, and many patients notice that carbohydrate food is particularly apt to produce symptoms. The true incidence of the condition is difficult to assess, because in the first few weeks after gastrectomy many patients experience these symptoms to a greater or less extent, but in the majority a spontaneous improvement occurs. The syndrome may also, but less often, develop after gastro-enterostomy.

It was shown by Machella (1949) that in patients with the dumping syndrome the symptoms could be reproduced by the ingestion of hypertonic glucose, sucrose, laevulose, and casein hydrolysate solutions, and that similar symptoms could be produced in the normal subject by the introduction of hypertonic glucose into the jejunum. Roberts *et al.* (1954), studying 14 patients who had undergone gastrectomy (10 total, 4 subtotal), showed that a suitably adjusted oral dose of any one of several hypertonic solutions produced with the dumping symptoms a simultaneous fall in plasma volume, and this was thought to be the main cause of the symptoms. They postulated that this fall in plasma volume was due to a transfer of fluid into the gut as a result of the osmotic attraction of the hypertonic solutions. They suggested that in the absence of the pylorus the unduly rapid passage of hyperosmotic food and its derivatives into the small intestine causes a shift of fluid from the vascular compartment with a fall in circulating volume, and this in turn causes the dumping symptoms.

If this hypothesis is true it is difficult to understand why all patients do not experience dumping symptoms after partial gastrectomy. Accordingly, to clarify the role of a fall in plasma volume in the production of symptoms we have not only investigated the effect of hypertonic glucose in the production of symptoms and a fall in plasma volume, but have also observed the individual's response to a reduction in circulating volume produced by the application of thigh cuffs. These investigations were carried out in two groups of patients: (*a*) 16 patients upon whom the test was performed before and at intervals after partial gastrectomy, and (*b*) 11 patients with the dumping syndrome. In some of these patients certain additional tests were also performed.

Plasma Volume Studies

The test was performed in the morning, with the patient semi-recumbent on a couch after eight to nine hours without food or drink. A 7-ml. sample of venous blood was taken, followed by intravenous injection of 4–6 g. of 0.5% aqueous solution of Evans blue. Further venous samples were taken 60 and 80 minutes later and immediately after the latter the subject drank, within one minute, 175 ml. of 50% glucose. Venous samples were taken at 10, 20, 30, 40, 60, 90, and 120 minutes thereafter, though in some cases the later samples were taken at slightly differing intervals.

The venous samples (7 ml.) were taken without stasis into siliconed syringes, and immediately transferred to tubes containing 7 units of dry heparin. The haematocrit of each sample was measured in a Wintrobe tube spun for 30 minutes at 3,000 r.p.m. in a governed centrifuge with an arm of 15 cm. radius to the bottom of the tube (1,500 g.). The remainder of each sample was spun to separate the plasma, in which the concentration of Evans blue was estimated in duplicate by a modification (Hobsley and Dew, 1958) of the extraction method of Korner *et al.* (1954). The apparent plasma volume at the time of each sample was calculated from the following formula, the standard being 1 : 500 dilution of the Evans blue solution:

$$\text{Pl. vol. (L)} = \frac{\text{standard reading} \times \text{dose given (g. 0.5\% E.B.)} \times 0.5}{\text{reading of sample}}$$

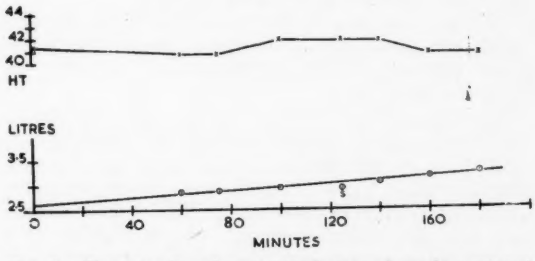


FIG. 1.—Haematocrit and apparent plasma volume in a normal man at rest. Evans blue injected intravenously at time zero. After 60 minutes Evans blue disappears from the plasma at a steady rate, giving a linear increase in the apparent plasma volume. Stagnation occurred while taking the 125-minute sample, giving a slightly inaccurate reading.

These values for the plasma volume were plotted against time. Under normal circumstances, between 60 and 200 minutes after the injection of Evans blue the plasma volume apparently increases in a linear fashion owing to the disappearance of dye from the plasma (Fig. 1). In our observations this line could be drawn by joining the first two and the last two points plotted, and any alteration in plasma volume after the ingestion of glucose was represented by a deviation of the other points away from this line. The size of the fall as a percentage of the resting plasma volume is given by the expression:

$$\frac{\text{apparent fall}}{\text{expected apparent plasma volume}} \times 100$$

An approximate estimate of the size of the change in plasma volume could also be obtained from the haematocrit readings by the application of the formula

$$x = \frac{Ht_1}{100-Ht_1} \times \frac{100-Ht_2}{Ht_2} \times 100$$

where x = the percentage of the original to which the plasma volume is reduced, Ht_1 the initial haematocrit reading, and Ht_2 that at the time of maximum fall of plasma volume.

Reduction of Circulatory Volume by Thigh Cuffing.—With the patient sitting upright in a chair, pneumatic tourniquets were applied to both thighs. Pulse and blood-pressure were recorded in one arm at five-minute intervals until they were stable. The thigh cuffs were then inflated to a pressure 20 mm. Hg below the brachial systolic pressure. Ten minutes later the pressure in the cuffs was raised a further 10 mm. Hg for 10 minutes and then the cuffs were deflated. Pulse and blood-pressure were recorded throughout and thereafter until they returned to normal; any abnormal symptoms occurring were also recorded.

Clinical Material

Series 1 consists of 16 patients studied before and after operation. These patients were admitted for subtotal gastrectomy and, save for excluding those with pyloric stenosis, were unselected. In each case the test involving the application of thigh cuffs was performed at some time during the week before operation. The effect of oral hypertonic glucose on the plasma volume was estimated before operation, at some time during the period 7–14 days after operation, again about six months later, and in two patients on an intermediate occasion as well about three months after operation. The pre-operative test was omitted in three cases, and the late post-operative in three others. Details of the patients in this group are given in Table I.

Series 2 consists of 11 patients with the dumping syndrome after previous gastric surgery. Details of these patients, who were investigated similarly, are given in Table II.

Throughout the remainder of this paper the estimation of the plasma volume after the oral administration of 175 ml. of 50% glucose is referred to as a "plasma volume study," the various tests being described respectively as pre-operative, and early, intermediate, and late post-operative plasma volume studies. The term "fall in plasma volume" refers to the maximum fall, which always occurred 10 to 20 minutes after the ingestion of the glucose solution. The test involving the inflation of pneumatic cuffs around the thighs is referred to as cuffing.

TABLE I.—*Details of 16 Patients in Series 1, and the Tests Performed on Them*

Case No.	Age and Sex	Lesion	Operation	Cuffing	Plasma Volume Studies			
					Pre-operative	Early	Intermediate	Late
1	54 M	D.U.	A.P.	Yes	Yes	Yes	No	Yes
2	65 F	G.U., D.U.	B.	,,	,,	,,	Yes	,,
3	52 M	D.U.	A.P.	,,	,,	,,	No	,,
4	32 M	D.U.	A.P.	,,	,,	,,	,,	,,
5	32 M	D.U.	A.P.	,,	,,	,,	,,	,,
6	39 M	D.U.	A.P.	,,	,,	,,	,,	,,
7	50 M	G.U.	B.	,,	,,	,,	,,	,,
8	50 M	D.U.	A.P.	,,	,,	,,	,,	,,
9	58 M	D.U.	A.P.	,,	No	,,	,,	,,
10	61 M	D.U.	A.P.	,,	Yes	,,	,,	,,
11	64 M	G.U.	B.	,,	,,	,,	,,	,,
12	40 M	D.U.	A.P.	,,	,,	,,	,,	,,
13	46 M	Carc.	R.P.	,,	,,	,,	,,	No
14	70 M	D.U.	A.P.	,,	,,	,,	,,	,,
15	20 M	D.U.	B.	,,	No	,,	Yes	Yes
16	46 M	G.U.	A.P.	,,	,,	,,	No	,,

A.P. = Antecolic, Polya. R.P. = Retrocolic, Polya. B. = Billroth I. All the Polya operations were performed with the afferent loop to the lesser curve and a valve on the lesser curve.

TABLE II.—*Details of 11 Patients in Series 2, and the Tests Performed on Them*

Case No.	Age and Sex	Lesion	Operation	Time after Operation	Cuffing	Plasma Volume Test
17	52 F	Ac. G.U.	B.	2·2 years	No	Yes
18	42 F	G.U.	P.	3 ,,	Yes	,,
19	49 M	G.U.	B.	15 months	,,	,,
20	58 F	D.U.	A.P.	12 ,,	,,	,,
21	48 M	D.U.	A.P.	5 ,,	,,	,,
22	62 F	D.U.	G–E	9 years	,,	,,
23	45 F	Ac. G.U.	A.P.	18 months	,,	,,
24	36 M	G.U.	B.	13 ,,	,,	,,
25	64 M	D.U.	A.P.	3 years	,,	,,
26	47 F	D.U.	A.P.	4 ,,	,,	,,
27	35 F	?	G–E	7 ,,	,,	,,

A.P. = Antecolic, Polya. B. = Billroth I. G–E = Gastro-enterostomy. The position of the loop in Case 18 was not known. See text for details of Case 27.

Results of Plasma Volume Studies

Pre-operative Studies.—Plasma volume studies were carried out before operation in 13 of the 16 patients in Series 1. In no case did the oral glucose cause any symptoms. The greatest fall in plasma volume observed was 7%, but usually it was less than 5%. Details are given in Table III, columns 3 and 4.

Post-operative Studies

Thirty-two plasma volume studies were carried out at the various times after operation in the 16 patients in Series 1 (see Table III). On eight occasions in four patients the hypertonic glucose produced typical dumping symptoms, and on all occasions at the time of these eight tests the patients were experiencing similar symptoms after their ordinary meals. On each occasion the symptoms coincided with the fall in plasma volume, which averaged 13.1% (range 8–20%). At the time of the remaining 24 tests no patient was experiencing post-prandial dumping symptoms, and none developed such symptoms after the glucose: the average fall in plasma volume in these tests was 7.2% (range 2–15%).

Early post-operative plasma volume studies were performed in all 16 patients. Four developed typical dumping symptoms within 15 minutes of drinking the glucose, the average fall of plasma volume in this group being 14.6%. The remaining 12 patients, who developed no symptoms, showed an average fall in plasma volume of 7.1%. Considering the results in relation to the size of the fall in plasma volume produced, four patients showed a fall of 10% or greater

TABLE III.—*Results of Various Tests Performed on Patients in Series 1. See Text for Grading of Results of Thigh-cuffing Tests*

Case No.	Thigh Cuffing	Plasma Volume Tests									
		Pre-operative		Early			Intermediate			Late		
		% Fall Plasma Volume		% Fall Plasma Volume		Symptoms	% Fall Plasma Volume		Symptoms	% Fall Plasma Volume		Symptoms
		E.B.	Ht.	E.B.	Ht.		E.B.	Ht.		E.B.	Ht.	
1	+	5·0	7·5	<3	4·0	0	—	—	—	7·0	7·5	0
2	++	<2	2·0	18·0	19·0	++	10·5	15·0	+	4·0	6·0	0
3	+	5·0	1·0	4·0	4·0	0	—	—	—	3·0	4·0	0
4	+	2·0	2·0	8·0	8·0	+	—	—	—	11·0	8·0	+
5	0	2·5	3·5	12·5	16·0	++	—	—	—	12·0	9·5	++
6	0	4·5	2·0	6·5	7·5	0	—	—	—	5·5	4·0	0
7	0	0	0	8·0	11·5	0	—	—	—	9·0	11·0	0
8	0	5·0	5·5	8·0	5·5	0	—	—	—	7·0	6·0	0
9	0	—	—	3·0	6·0	0	—	—	—	5·5	4·0	0
10	0	7·0	6·0	6·0	6·0	0	—	—	—	9·5	10·0	0
11	0	4·0	5·0	9·0	11·0	0	—	—	—	8·0	9·0	0
12	0	7·0	4·0	9·0	8·0	0	—	—	—	10·0	10·0	0
13	+	3·5	4·0	7·0	8·0	0	—	—	—	—	—	—
14	0	4·0	5·0	8·0	11·0	0	—	—	—	—	—	—
15	+	—	—	20·0	14·0	++	12·5	10·0	+	5·0	5·5	0
16	0	—	—	15·0	16·5	0	—	—	—	13·0	13·0	0

E.B. = Fall in plasma volume as measured by Evans blue. Ht. = Fall in plasma volume calculated from haematocrit.

and three of these had symptoms. In 12 patients the fall was less than 10%, and of these only one had symptoms.

A late post-operative plasma volume study was performed on all but two (Cases 13 and 14) of the patients. The test was performed on 10 of the 12 patients who had no symptoms at the early test: none had symptoms on the late test, and there was no significant change in the fall in plasma volume (correlation coefficient = 0.80; regression coefficient = 1.055). Of the four patients who had symptoms after the early test, two (Cases 4 and 5) had not improved clinically by the time of the late test; in both these patients the late test again produced typical dumping symptoms and a fall in plasma volume of the same magnitude as at the early test. The results in Case 5 are illustrated in Fig. 2. The remaining two (Cases 2 and

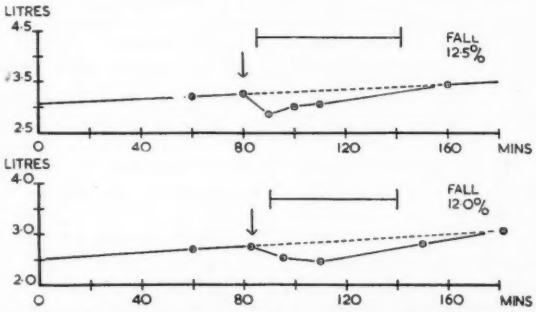


FIG. 2.—Case 5. Graphs showing the fall in plasma volume after hypertonic glucose on early and late post-operative testing. Shortly after operation this patient began to experience typical post-cibal dumping symptoms, which did not improve with the passage of time. On each occasion the hypertonic glucose reproduced identical symptoms, the duration of which is shown by the line above the plasma volume curve. The fall in plasma volume is the same on each occasion. In this and subsequent diagrams the vertical arrow denotes the time at which the glucose was drunk.

15) had spontaneously recovered from their dumping syndrome before the time of the late test, and in each an intermediate test was performed at a time when recovery was only partial. Results in both cases were similar. The early test produced severe symptoms and a large fall in plasma volume (18% and 20% respectively), the intermediate test had less severe but still definite symptoms with smaller falls in plasma volume (10.5% and 12.5%), and at the late test the glucose produced no symptoms and minimal falls in plasma volume (4% and 5%). The results of the plasma volume tests on one of these patients (Case 2) are shown in Fig. 3.

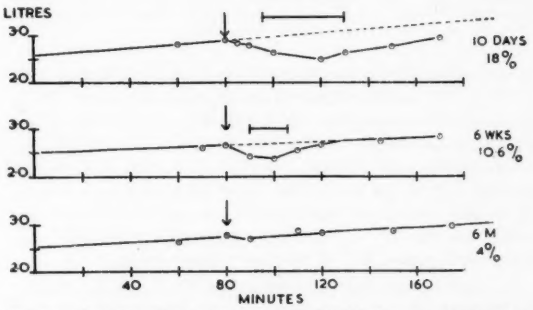


FIG. 3.—Case 2. Graphs showing the fall in plasma volume after hypertonic glucose on early, intermediate, and late post-operative testing. Shortly after operation this patient experienced typical post-cibal dumping symptoms, which soon began to improve and had disappeared by the time of the last test. The hypertonic glucose produced a progressively smaller fall in plasma volume and progressively fewer symptoms as the clinical condition regressed.

Plasma volume studies were carried out in the 11 patients of Series 2 (see Table IV). In all but one (Case 25) the hypertonic glucose produced symptoms identical with those the patients were experiencing after meals. In all these 10 patients symptoms coincided with a fall in plasma volume, which in nine was at least 10% and

TABLE IV.—*Results of Various Tests Performed on Patients in Series 2*

No.	Cuffing	Plasma Volume Test		
		% Fall		Symptoms
		E.B.	Ht.	
17	—	16·0	15·5	+
18	+	12·5	12·0	+
19	0	16·0	14·5	+
20	+	11·0	10·0	+
21	+	11·0	9·5	+
22	++	12·0	6·0	++
23	+	10·0	13·0	+
24	+	10·0	9·0	—
25	0	11·0	11·5	0
26	++	7·5	12·0	++
27	++	14·5	10·5	++

in the 10th 7.5%; the average fall was 11.8% (range 7.5–16%). A typical result from one of these patients is shown in Fig. 4.

Case 27 is of particular interest, as in this patient circumstances allowed us to observe the effect of closing a gastro-enterostomy. Seven years previously this young woman had undergone a gastro-enterostomy elsewhere, for unknown reasons. Since that time she had experienced severe dumping symptoms and had lost 20 lb. (9 kg.) in weight. Hypertonic glucose reproduced her symptoms, with a fall in plasma volume of 14.5%.

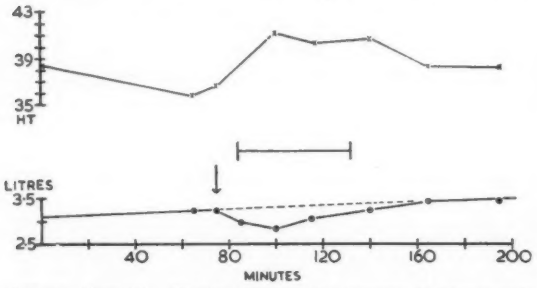


FIG. 4.—Case 18. Graphs showing the increase in haematocrit and fall in plasma volume after hypertonic glucose in one of the patients with an established dumping syndrome. The test produced typical symptoms, the duration of which is shown by the horizontal line. The fall in plasma volume as shown by direct measurement was 12.5% and as calculated from the change in haematocrit was 12%.

A barium-meal examination showed no evidence of any abnormality in the stomach or duodenum, apart from the gastro-enterostomy. At operation no evidence of a gastric or duodenal ulcer was found and the gastro-enterostomy was closed. Since then she has eaten normally with no post-cibal symptoms and has gained 10 lb. (4.5 kg.) in weight in seven months. Nine weeks after operation hypertonic glucose produced no symptoms, and a fall in plasma volume of only 4%.

In both series together, plasma volume studies were performed at varying times after operation on 43* occasions in 27 patients. Twenty-five times the test produced no symptoms and an average fall in plasma volume of 7.2% (range 2–15%) (S.D. 3.1). On only one of these occasions was the patient experiencing dumping symptoms after ordinary meals, and this exception (Case 25) is described in detail below. On the remaining 18 occasions the test produced typical symptoms with an average fall in plasma volume of 12.5% (range 7.5–20%) (S.D. 3.32), and all the patients were, at the time of testing, experiencing dumping symptoms after meals. The difference in the fall in plasma volume between these two groups is highly significant ($t=4.84$; $n=40$; $p<0.001$). It is to be noted, however, that there is a clear overlap between the two groups, with no absolute correlation between the occurrence of symptoms and the size of the plasma volume fall.

Cuffing Test

In Series 1 the cuffing test was performed on all patients. In 10 patients it produced no symptoms except locally in the legs. In the remaining six inflation of the cuffs produced, after a varying interval, faintness, drowsiness, and sweating, progressing in one case to complete loss of consciousness with disappearance of the radial pulse, necessitating termination of the test. The results in each case are shown in Table III, column 2. For recording purposes the severity of the response was classified into three grades: grade O no symptoms; grade +, definite symptoms; grade ++, severe symptoms, necessitating termination of the test. No clear correlation was noticed between the development of symptoms and alterations in pulse-rate and blood-pressure. These latter were so variable both in those who did and in those who did not experience symptoms that they are not reported here.

In Series 2 the cuffing test was performed on 10 of the 11 patients (Table IV, column 2). In two patients it produced no symptoms: one of these is Case 25, discussed below. Five of the remaining eight patients had definite symptoms and three had severe symptoms.

In both series together, the test was performed on 26 patients. The result was negative in 12 and positive in 14. It is to be noted that of these 14 patients 11 had dumping symptoms after the hypertonic glucose, while only 2 of the 12 who had no symptoms on cuffing had symptoms after the glucose. The significance of these observations is discussed later, but of particular importance in this respect are the detailed findings in Case 25.

Case 25.—A man aged 64 underwent a partial gastrectomy for a chronic duodenal ulcer three years ago. Ever since, he has been restricted to small meals by a feeling of epigastric distension, followed by exhaustion, causing him to lie down and sleep for 15 to 20 minutes. These attacks follow all but the smallest meals, and after severe attacks he passes a loose motion. 175 ml. of 50% glucose by mouth produced a fall in plasma volume of 11.5%, but no symptoms. However, 225 ml. of 50% glucose also given with the patient in a semi-recumbent position reproduced his postprandial symptoms and caused a fall in plasma volume of 14.5%. Cuffing did not produce symptoms, neither did 175 ml. of 50% glucose taken sitting in a chair. However, when this quantity of glucose was taken sitting, with the simultaneous performance of a cuffing test, marked symptoms of faintness and exhaustion, worse than those following a meal, came on after 12 minutes. These symptoms were quickly relieved by deflating the cuffs and raising the patient's legs.

Plasma Volume Studies After a Meal

In two patients in Series 2 (Cases 20 and 26), in whom the fall in plasma volume after hypertonic glucose was respectively 11% and 7.5%, changes in plasma volume were also measured after a meal. In each instance the patient was sitting at a table throughout the procedure, which was the same as that previously described except that a meal was taken instead of hypertonic glucose. The meal was of the breakfast type (cornflakes, toast, tea, sugar, fruit juice, milk, marmalade) with carbohydrate predominating. In each case the size of the meal was the maximum that the patient could eat,

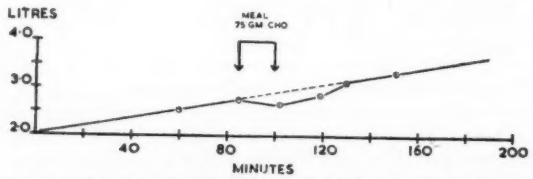


FIG. 5.—Case 20. Graph showing a fall in plasma volume of 11% after eating a meal containing 75 g. of carbohydrate. After the standard dose of hypertonic glucose this patient had a fall in plasma volume of 11%.

*This total includes only the first of two tests performed in Case 27, as the second was done after closure of the gastro-enterostomy.

and in each case it produced marked symptoms. The patient in Case 20 took a meal containing 75 g. of carbohydrate in 15 minutes, and in Case 26, 55 g. in 10 minutes. After the meal each patient experienced typical marked dumping symptoms, which coincided with falls in plasma volume of 11% and 8% respectively. Fig. 5 shows the results obtained in Case 20.

Replacement Infusion Experiments

On four occasions in three patients from Series 2 an intravenous infusion was given after the ingestion of 175 ml. of 50% dextrose. All three patients had had typical symptoms during a standard plasma volume study. The volume infused was equal to the fall in plasma volume observed during this previous study. The infusion was started immediately on drinking the glucose and was completed in 10 to 15 minutes, a Martin pump being used to obtain the necessary infusion-rate.

In Case 17, on the first occasion 250 ml. of normal saline was infused in 10 minutes without affecting the symptoms. When the experiment was repeated four days later using dextran (" dextraven ") instead of normal saline the patient experienced no systemic symptoms such as dizziness, sweating, and exhaustion, only slight nausea and upper abdominal discomfort. Case 19 was given 400 ml. of dextran in 15 minutes and experienced no symptoms. The third patient (Case 22) was given 300 ml. of dextran in 10 mins, resulting in partial but definite alteration of symptoms, especially in that she experienced no palpitations, sweating, or tiredness.

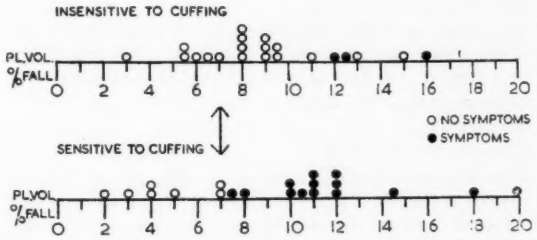
Discussion

Many observers have reported that in patients with the dumping syndrome the symptoms can be reproduced by the oral administration of hypertonic glucose. Our observations have confirmed this, and a standard dose of hypertonic glucose has been used as the basis of an investigation designed to test the hypothesis that the major factor in the production of these symptoms is a temporary fall in the plasma volume.

In general our results support this hypothesis. The average fall in plasma volume in those patients who had symptoms after the hypertonic glucose was significantly greater than in those patients who did not, though there was a distinct overlap between the two groups. Emphasizing this lack of correlation, Webber *et al.* (1957) concluded that a fall in plasma volume is not " a significant factor in the aetiology of the dumping syndrome." However, three of our observations make it difficult to accept this conclusion. First, in three patients experiencing typical symptoms after the test dose of glucose, the rapid intravenous infusion of an appropriate volume of a plasma expander prevented the development of systemic symptoms. Secondly, case 27, while experiencing dumping symptoms, had a fall in plasma volume of 14.5% after the test dose of glucose ; after closure of her gastro-enterostomy, which cured her symptoms, this fall was reduced to 4%. Thirdly, in two patients the spontaneous regression of the dumping syndrome during six to eight months following operation was accompanied by a progressive diminution in the fall in plasma volume after the test dose of glucose. These facts suggest that the symptoms are indeed caused by a fall in plasma volume, and that a further factor must be sought to account for the discrepancies.

The results of the thigh-cuffing experiments suggest that this factor is the individual variation in the response to a sudden fall in circulatory volume. The application of pneumatic cuffs to the thighs traps 400–700 ml. of blood in the legs in 15 to 20 minutes, and this produces the same effect as the venesection of an equal quantity of blood (McMichael and Sharpey-Schafer, 1944). By the use of this test it was possible to assess the response of our patients to a sudden fall in circulatory volume of a size similar to that produced in many by the oral hypertonic glucose.

The application of thigh cuffs showed that 12 patients were insensitive to a sudden reduction in circulating volume. Twenty-one post-operative plasma volume tests were performed on these patients, the falls observed varying between 3 and 16%. Only two of these patients (Cases 5 and 19) had symptoms after the glucose, and, on the three occasions of testing, their fall in plasma volume was 12.5%, 12%, and 16%. Fourteen patients were sensitive to thigh cuffing, four to the extent that the test had to be cut short. Twenty-two post-operative plasma volume tests were performed on this group of patients, the falls in plasma volume varying between 3 and 20%. On 14 occasions the glucose produced typical symptoms with falls in plasma volume of 7.5–20% ; on the remaining eight occasions the falls ranged between 3 and 7%. In other words, regardless of the patient's response to cuffing, a small fall in plasma volume (not greater than 7%) was never accompanied by symptoms, whereas if the fall was large (greater than 7%) symptoms always occurred in those sensitive to cuffing, and, except for two patients, never in those insensitive (Fig. 6). Presumably in these two patients the cuffing did not produce a fall in plasma volume as great as did the glucose.


INSENSITIVE TO CUFFING
PL.VOL. % FALL
0 2 4 6 8 10 12 14 16 18 20
O NO SYMPTOMS
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0 2 4 6 8 10 12 14 16 18 20

FIG. 6.—Diagram showing the relationship between, on the one hand, the sensitivity of the patient to a sudden reduction in circulating volume (by thigh cuffs) and, on the other, the size of the fall in plasma volume and the production of symptoms after hypertonic glucose. Each symbol represents not a patient but a single post-operative plasma-volume test, and blocking of the symbol indicates that the test produced symptoms. The upper line represents the results in those patients insensitive to cuffing, the lower in those sensitive. When the fall in plasma volume is small symptoms never occur, irrespective of the response to cuffing. When the fall is larger (7%) symptoms always occurred in those sensitive to cuffing, but with three exceptions (in two patients) not in those insensitive.

It would therefore appear that the development of symptoms after hypertonic glucose depends upon the interaction of two factors, the size of the fall in plasma volume and the resistance of the patient to such a fall. This is illustrated well by two individual cases. In Case 16 the patient had no symptoms on thigh cuffing and no symptoms with his early and late post-operative plasma volume tests, despite falls in plasma volume of respectively 15% and 13% ; he had no post-cibal

symptoms. In contrast, in Case 26 thigh cuffing produced definite symptoms within two minutes and had to be cut short at eight minutes as the patient was pale, sweating, and greatly distressed; a plasma volume test produced severe symptoms though a fall in plasma volume of only 7.5%; she had severe post-cibal dumping symptoms. This interaction between the size of the fall in plasma volume and the patient's ability to withstand such a fall is further emphasized by the studies in Case 25. This man was resistant to the fall in plasma volume produced by cuffing or the standard dose of hypertonic glucose, but when a large enough fall was achieved by a combination of these methods or by increasing the dose of glucose typical symptoms ensued.

Heretofore the occurrence of symptoms has been correlated with changes in plasma volume, though the precise factor involved must be a change in total blood volume. The difference between these two is probably small, as shown by the haematocrit estimations. On the assumption that there was no change in the circulating red-cell volume, alterations in plasma volume calculated from changes in the haematocrit corresponded fairly closely to those derived from the Evans blue estimations. However, conclusions concerning alterations in the total blood volume based on haematocrit and plasma volume readings are difficult to interpret (Mollison, 1956). For these reasons the production of symptoms has been correlated with fall in plasma volume, which can be measured accurately.

Though hypertonic glucose is an artificial stimulus, it is clear from our observations on two patients after a normal meal that the meal and the glucose produce similar falls in plasma volume with similar symptoms. As shown, these symptoms can be largely prevented by a suitable replacement infusion, and it may be concluded that the systemic symptoms of the dumping syndrome as seen clinically are due to a temporary post-cibal fall in circulating volume in patients sensitive to such a fall. There can be no reasonable doubt that this fall is due to a transfer of fluid into the intestines as the result of osmotic forces, as there is direct proof that such a transfer occurs when hypertonic glucose is introduced into the human intestine (Abbott *et al.*, 1938).

As our pre-operative tests show, the introduction of hyperosmotic solutions into the stomach causes only minimal falls in plasma volume. The reason for this is twofold: first, hyperosmotic solutions are only diluted slowly while in the stomach (Hunt *et al.*, 1951); and, secondly, such solutions delay gastric emptying, as first shown by Carnot and Chassevant (1905) working on dogs, and confirmed in humans by, amongst others, Apperly (1926). The resulting slow depletion of the plasma volume is readily compensated by a passage of fluid from the interstitial space. It would therefore appear that interference with the normal control of gastric emptying is the essential factor in the causation of the dumping syndrome.

Our observations lead to the conclusion that the symptoms of the dumping syndrome are due to the passage of an hyperosmotic solution into the upper intestine, causing in some patients a rapid transfer of fluid from the vascular compartment into the gut; this results, on the one hand, in intestinal distension and, on the other, in an abrupt fall in circulating volume which, in subjects intolerant of such a fall, gives rise to the systemic symptoms. This hypothesis provides a clear explanation of the well-established clinical features of the syndrome. The increase in fluid in the gut is responsible for the feeling of repletion and distension, with excessive peristalsis (Glazebrook and Welbourn, 1952) and, in severe cases, the passage of a loose stool. The fall in plasma volume is responsible for the faintness and exhaustion with pallor, sweating, and palpitations, thus explaining why these symptoms are relieved by reclining or lying, and are less prominent if the meal is eaten in a recumbent position. Obviously the greater the size of the meal the greater the osmotic load and so the worse the symptoms: it is for this reason that patients can take only small meals, and undoubtedly this is a major factor in their characteristic loss of or failure to gain weight. Apart from its actual size, the tendency of a meal to produce dumping symptoms also depends upon its osmolarity when in solution. This explains why carbohydrate, which is rapidly broken down into a large number of small glucose molecules with a corresponding rise in osmotic pressure, is particularly associated with the syndrome.

It remains to explain why, following a gastrectomy, only some patients show a fall in plasma volume after taking hypertonic glucose, and also why, in those who spontaneously recover from the dumping syndrome, this fall diminishes *pari passu*. These two facts are probably related to the rate at which glucose is absorbed from the intestine, and are considered in a further article.

Summary and Conclusions

The effects of oral hypertonic glucose in producing dumping symptoms and changes in plasma volume were observed in two groups of patients: (*a*) 16 patients undergoing partial gastrectomy, in whom the test was performed before and at intervals after operation; and (*b*) 11 patients with the dumping syndrome. In all but one patient the effect of a sudden reduction in circulatory volume by the application of thigh cuffs was also observed.

In all but one of the patients who at the time of testing were experiencing post-cibal dumping symptoms the hypertonic glucose reproduced these symptoms; the glucose never produced symptoms in those who were symptom-free after meals.

The hypertonic glucose produced a fall in plasma volume which was significantly greater in those with than those without symptoms, but there was a definite overlap between the two groups. The results of the thigh-cuffing observations showed that this overlap was due to the differences in the individual response to a sudden fall in circulatory volume.

Additional evidence linking the systemic symptoms of the dumping syndrome with the fall in plasma volume was provided by replacement infusion experiments, by observations on two patients who spontaneously recovered from the syndrome, and by observations on a patient before and after closure of a gastro-enterostomy.

It is concluded that the dumping syndrome is due to the passage of hyperosmotic solutions into the upper intestine, causing in some patients a rapid transfer of fluid from the vascular compartment into the intestine. This results in intestinal distension and an abrupt fall

in circulating volume, which, in subjects intolerant of such a fall, gives rise to the systemic symptoms.

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THE DUMPING SYNDROME

II. CAUSE OF THE SYNDROME AND THE RATIONALE OF ITS TREATMENT

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In the previous communication the role of a fall in plasma volume in the production of the dumping syndrome was described (Le Quesne *et al.*, 1960). It was shown that the fall in plasma volume following the ingestion of hypertonic glucose by patients who had undergone partial gastrectomy varies greatly from individual to individual, and in some with the passage of time. It was further shown that the development of symptoms depends not only upon the size of the fall in plasma volume but also upon the individual's response to a sudden reduction in circulating volume. In the course of these studies we noted that the coincident changes in blood-sugar concentration were far from constant. In the present paper we propose to examine the relation of the changes in blood-sugar concentration to those in plasma volume, and to describe further observations, made after the injection of insulin, which clarify this relationship. From these observations we have been able to devise means, by the use of insulin, of reducing the fall in plasma volume produced by hypertonic glucose or by meals, and thus of relieving the dumping syndrome.

Procedure and Material

Changes in plasma volume and blood-sugar concentration were estimated after the drinking of 175 ml. of 50% glucose. The test involved the taking of venous samples before and at 10 minutes after taking the glucose, and at varying intervals thereafter. Details of the conditions of the test have been given previously (Le Quesne *et al.*, 1960).

Observations were also made of the effects of the prior injection of insulin on the changes in plasma volume following (*a*) 175 ml. of 50% glucose by mouth, and (*b*) a carbohydrate meal.

The change in plasma volume was estimated by the use of Evans blue: details of the methods involved are given in our previous communication. The blood-sugar concentration was measured by the method of Haslewood and Strookman (1939), as described by Varley (1958).

Changes in plasma volume and blood-sugar concentration were estimated on 35 occasions in 28 patients, who fell into two groups. Group A consists of 13 patients admitted to the wards of the department for subtotal gastrectomy for benign peptic ulcer. These patients are the same as those in Series 1 in our previous paper, in which full details concerning them are given; Cases 4, 11, and 12 are omitted here, as blood-sugar estimations in them are not available. In the 13 patients post-operative studies were performed on 26 occasions; on seven of these the blood glucose was not estimated, leaving 19 for analysis here. Group B consists of 15 patients admitted for investigation of their dumping syndrome: in 14 this followed partial gastrectomy and in one a gastro-enterostomy. Of these 15 patients, seven form part of Series 2 in our previous communication; Cases 17, 20, 23, and 26 are omitted because again blood-sugar estimations are not available. Details of the remaining eight patients are given in Table I.

TABLE I.—*Details of the Eight Patients in Group B Additional to Those Described in Our Previous Communication*

Case No.	Age	Sex	Lesion	Operation	Time after Operation
28	53	F	G.U.	B.	7 months
29	73	M	D.U.	A.P.	26 ,,
30	47	M	Carc.	T.G.	5 years
31	54	M	G.U., D.U.	A.P.	5 ,,
32	71	F	D.U.	B.	3 ,,
33	43	M	D.U.	A.P.	2 ,,
34	55	F	Chol.	A.P.	8 months
35	77	M	D.U.	P. & V.	5 ,,

G.U. = Gastric ulcer. D.U. = Duodenal ulcer. Chol. = Recurrent cholangitis, from choledocho-duodenal fistula. B. = Billroth I gastrectomy. A.P. = Antecolic Polya gastrectomy. T.G. = Total gastrectomy. P.&V. = Pylorectomy and vagotomy.

The effect of the prior injection of insulin was observed in seven patients following the ingestion of 175 ml. of 50% glucose, and in three patients following a carbohydrate meal. Of these 10 patients, seven were drawn from those described in our previous paragraph. The remaining three (Cases 38, 43, and 44) were admitted for investigation of their dumping syndrome: in two (Cases 38 and 43) the fall in plasma volume was calculated from changes in the haematocrit (see previous paper) and not by direct measurement.

Observations on Blood Sugar and Plasma Volume

After ingestion of the test dose of 175 ml. of 50% dextrose it was noted that the greater the fall in plasma volume the more rapid and pronounced was the rise in blood sugar. Typical blood-sugar curves associated with a large and small fall in plasma volume are shown in Fig. 1.

The data on blood sugar and plasma volume for all the patients were analysed in various ways in an attempt to discover any correlation between the two. No correlation could be found between, on the one hand, either the greatest height to which the blood sugar rose or the time taken to return to its resting level, and, on the other, the fall in plasma volume. There is, however, a clear correlation between the fall in plasma volume

and the rate at which the blood-sugar concentration rises shortly after drinking the hypertonic glucose. An index of this rate is provided by expressing the blood-sugar concentration 10 minutes after the ingestion of glucose as a percentage of the concentration at zero time. If this figure is plotted against the maximum percentage fall in plasma volume (Fig. 2) a direct linear correlation is found (correlation coefficient +0.863 : $P<0.000000001$).

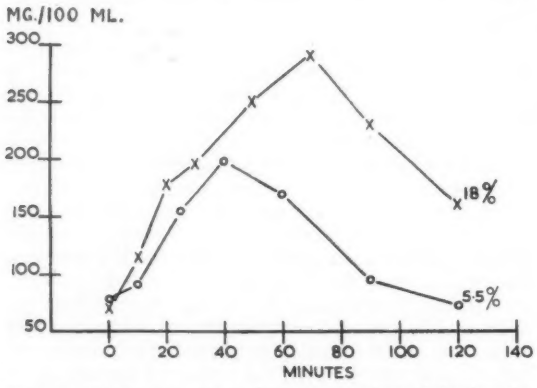

FIG. 1.—Blood-sugar curves from two patients following the ingestion of 175 ml. of 50% glucose. In one (Case 2) the fall in plasma volume was large (18%), while in the other (Case 6) it was small (5.5%).

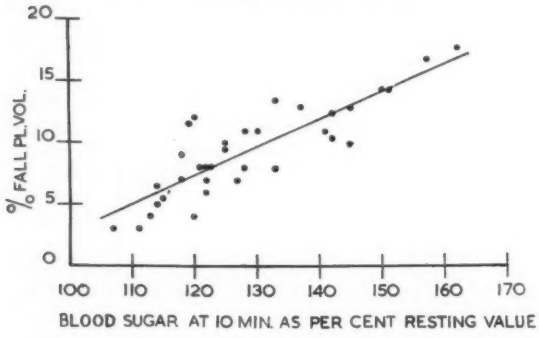

FIG. 2.—Graph showing the relationship between the maximum percentage fall in plasma volume following the ingestion of 175 ml. of 50% glucose and the rate of rise of the blood-sugar concentration, measured by expressing the concentration at 10 minutes as a percentage of that at zero time (resting value). Each point represents a single test, and the results from every test are included. The line drawn satisfies the following regression equation: $y=0.23x-20.3$, where x = the blood-sugar concentration at 10 minutes as a percentage of that at zero time, and y = the maximum percentage fall in plasma volume.

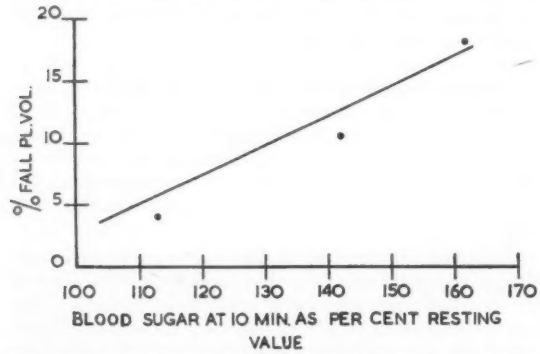

FIG. 3.—Graph showing the relationship between the maximum percentage fall in plasma volume and the rate of rise of the blood-sugar concentration for each of the three tests performed in Case 2. The oblique line is the regression line from the previous figure.

The relationship between these two factors is even more clearly shown by the results in Case 2. In the early days after her gastrectomy this patient had severe dumping symptoms, which spontaneously cleared up in the ensuing six months. Plasma volume studies were performed on this patient shortly after operation and three months and six months later. Fig. 3 shows the points obtained by plotting the maximum percentage fall in plasma volume against the rate of rise of the blood-sugar concentration for each of these three studies.

Effects of Insulin Administration

Experiments were performed to see whether lowering of the blood-sugar concentration by the prior injection of insulin affected the fall in plasma volume following the drinking of hypertonic glucose. In six patients the fall in plasma volume was measured after 175 ml. of 50% dextrose, and in one patient after 125 ml. This observation was then repeated after a subcutaneous injection of soluble insulin which was intended to lower the blood-sugar concentration to about 50 mg./100 ml.

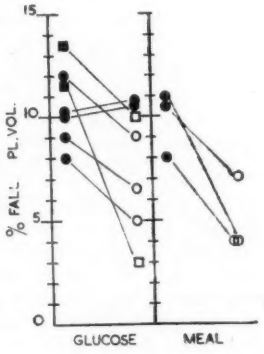

FIG. 4.—Graph showing the effect of the prior injection of insulin on the maximum percentage fall in plasma volume following ingestion of 175 ml. of 50% dextrose or of a carbohydrate meal. The pair of observations on each patient are linked by a straight line, the left-hand point representing the study without insulin and that on the right the study with insulin. Blocked symbols indicate that the test produced dumping symptoms, while clear ones indicate a lessening or absence of symptoms. Square symbols indicate that the change in plasma volume was calculated from the change in haematocrit, while in those with circles it was measured by Evans blue.

The dosage and timing of the insulin injection, based on the results of a previous subcutaneous insulin tolerance test, are given in Table II, together with the blood-sugar level achieved, and the fall in plasma volume on each of the two tests. In five patients the prior injection of insulin lessened the fall in plasma volume and in two the fall was unchanged (Fig. 4).

TABLE II.—*Details of the Insulin Studies*

Case No.	Stimulus		% Fall in Plasma Volume			Insulin		
	Type	CHO Content (g.)	How Measured	Without Insulin	With Insulin	Dosage. Units, Soluble	Time before Stimulus (min.)	Blood Sugar Reduced to (mg. 100 ml.)
5	G1	87·5	E.B.	12	9	15	75	61
23	G1	87·5	E.B.	10	10·5	12·5	60	58
24	G1	87·5	E.B.	10	10·5	15	65	59
33	G1	87·5	E.B.	8	5	10	50	72
34	G1	62·5	E.B.	9	6·5	10	80	45
38	G1	87·5	Ht.	13·5	10	10	60	58
43	G1	87·5	Ht.	11·5	3	10	80	45
20	M	75	E.B.	11	4	25	55	60
26	M	55	E.B.	8	4	10	50	—
44	M	89	E.B.	11	7	15	60	53

G1 = 175 ml. of 50% dextrose. M = Carbohydrate-rich meal. E.B. = Evans blue. Ht. = Haematocrit.

In three other patients similar observations were carried out after the stimulus of a breakfast type meal rich in carbohydrate, instead of the hypertonic glucose. In each instance the size of the meal was such as had been found by previous observation to be the largest the patient would take. In all three patients the insulin lessened the fall in plasma volume (Table II ; Fig. 4).

All 10 patients on whom this insulin test was performed were suffering from the dumping syndrome, and in each the hypertonic glucose or carbohydrate meal reproduced their symptoms. In all those patients in whom the insulin caused a lessening of the fall in plasma volume the symptoms were distinctly less: in all three cases after the meal and in two cases (Nos. 33 and 34) after the glucose the symptoms were completely prevented by the insulin.

No correlation could be found between the level to which the blood-sugar concentration had been lowered by the insulin and the extent to which the fall in plasma volume was affected. But it was found that in those cases in which the fall in plasma volume was distinctly less the blood-sugar curve was much lower throughout the 2½-hour period of observation. One such pair of curves is shown in Fig. 5.

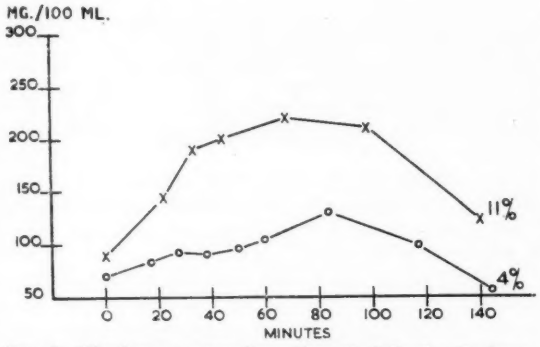

FIG. 5.—Blood-sugar curves from Case 20, following the ingestion of a meal containing 75 g. of carbohydrate, with and without the prior injection of 25 units of soluble insulin. Without insulin (×——×) the meal produced marked dumping symptoms and a fall in plasma volume of 11%; after insulin (O——O) there were no symptoms and a fall of only 4%.

In Case 26 the prior subcutaneous injection of insulin permitted the patient to eat a carbohydrate meal without symptoms, and reduced the fall in plasma volume from 8% to 4%. However, when 5 units (0.1 unit/kg. body weight) were injected intravenously five minutes before starting an exactly similar meal the onset of severe dumping symptoms prevented her finishing the meal.

Discussion

It is well established that after partial gastrectomy many patients have an abnormal response to a glucose-tolerance test, the blood-sugar curve showing a rapid rise, an abnormally high maximum level, and often a subsequent fall to abnormally low levels (Adlersberg and Hammerschlag, 1947 ; Gilbert and Dunlop, 1947). This type of curve is often called the lag curve. It is also known that after partial gastrectomy the ingestion of hypertonic glucose causes a variable fall in plasma volume as the result of an osmotic transfer of fluid into the intestine. The results reported here show that there is a close correlation between these two phenomena, and that the larger falls in plasma volume occur in those patients showing a lag type of blood-sugar curve. Further, there is a direct relation between the size of the fall in the plasma volume and the initial rate of rise of the blood-sugar curve. Any explanation of the abnormal glucose-tolerance curve must therefore also be capable of explaining why it is associated with a large fall in plasma volume.

The usual explanation of this abnormal glucose-tolerance curve is that, in those subjects in whom it occurs, there is excessively rapid emptying of the gastric remnant: this results in a very rapid presentation of glucose to the small intestine, a rapid absorption, and hence a rapid increase in blood-sugar concentration. This explanation could obviously account for the close correlation between the initial rate of rise of the blood-sugar concentration and the extent of the fall in plasma volume, in that the more rapid the gastric emptying the greater must be the osmotic force exerted in the small intestine. In other words, this explanation postulates that the basic difference between those patients who do and do not have a large fall in plasma volume is the rate at which the gastric remnant empties. No immediate reason is apparent why in some patients the gastric remnant should empty faster than in others.

There is, however, an alternative explanation. Following the oral administration of glucose, even after gastrectomy, the shape of the blood-sugar curve must depend upon the balance between the rate of absorption of glucose from the intestine and the rate of removal of glucose from the blood-stream. It may be that in patients with the lag type of curve the rapid rise of the blood-sugar curve is due to slow removal of glucose from the blood-stream, and that the resultant high blood-sugar concentration results in a slowing of absorption due to interference with diffusion processes. This slowing of the absorption of glucose will result in a considerable osmotic shift of fluid into the intestine, so increasing the fall in plasma volume, and, as a result of the increase of fluid in the gut, stimulating intestinal peristalsis. This in turn will increase the rate of emptying of the gastric remnant, so increasing the osmotic load in the intestine and setting up a vicious circle. This alternative hypothesis postulates that the basic difference between those who do and those who do not have a large fall in plasma volume lies in their ability to metabolize absorbed glucose, and that the difference in gastric emptying is a secondary phenomenon.

This latter hypothesis depends upon the assumption that after gastrectomy the emptying rate of the gastric remnant depends not upon its own intrinsic muscular activity but upon jejunal or duodenal peristalsis, and further, that intestinal peristalsis is increased in those with the dumping syndrome. It is difficult to find direct evidence upon the first of these points, but on the basis of their observations Vitkin (1940), Bruusgaard (1946), and Porter and Claman (1949) all suggest that jejunal contraction is a factor of major importance in gastric emptying after partial gastrectomy. As regards the second point, it is well established that in patients with the dumping syndrome there is increased intestinal peristalsis (Glazebrook and Welbourn, 1952).

Either of the two hypotheses outlined above demands that the emptying rate of the gastric remnant is faster in those patients with the dumping syndrome. That this is true has been shown with meals by Abbott *et al.* (1958) and with hypertonic glucose by Amdrup *et al.*

(1958). At present it does not seem possible to decide whether this is a primary or a secondary phenomenon. However, the following considerations support the second hypothesis—namely, that glucose metabolism is the factor of major importance.

1. The dumping syndrome affects many patients in the early weeks after partial gastrectomy, but in the majority it disappears spontaneously. This recovery must represent an adaptation to the altered gastro-intestinal conditions. As it is the distal portion of the stomach, the part which controls the emptying rate of the intact organ (Thomas, 1957), that has been removed, it is difficult to believe that this adaptation depends solely upon an alteration in the rate at which the gastric remnant empties itself.

2. Lundh (1958) has shown that while, in general, glucose absorption is within normal limits after partial gastrectomy, it is impaired in those cases in which the intestinal transit is extremely rapid. Lundh did not correlate the rate of glucose absorption with the presence or absence of dumping symptoms, but an exceptionally rapid intestinal transit is a known feature of the dumping syndrome (Amdrup *et al.*, 1958). Further, as shown above, the dumping syndrome is associated with a rapidly climbing glucose-tolerance curve, which is therefore occurring in the presence of impaired absorption.

3. As our insulin studies show, the fall in plasma volume after the ingestion of hypertonic glucose, and hence presumably the osmotic transfer of fluid into the intestine, can be diminished by accelerating carbohydrate metabolism. The effect of the insulin must be due to an increase in rate of glucose absorption, probably as the result of facilitating diffusion processes. From an examination of the blood-sugar curves after giving insulin it is clear that this is not due to an alteration in intestinal membrane permeability, as the insulin produces a lower blood-sugar curve. Probably the effect is due to an increased rate of removal of glucose from the blood-stream. Whatever the exact mechanism by which it works, the clinical significance of the effect of insulin lies in the fact that by altering carbohydrate metabolism the fall in plasma volume occurring after hypertonic glucose can be modified.

Two further points concerning the insulin studies require comment. First, the observation that insulin given intravenously immediately before a meal has no effect as opposed to an equivalent subcutaneous dose given some time previously shows that the insulin must work not by its mere presence in the blood-stream but by an indirect effect, presumably on carbohydrate metabolism, which takes time to develop. Secondly, in general, insulin was more effective, both in lowering the fall in plasma volume and in preventing symptoms, when given before a meal than when given before hypertonic glucose. This is probably due to two factors: (*a*) except in one case, the carbohydrate content of the meal was lower than that of the hypertonic glucose; and (*b*) whereas the glucose was drunk in less than one minute, the meal took five to seven minutes to consume, and, further, some of the carbohydrate in the meal was in the form of starch, which requires a little time for its digestion into osmotically active glucose. As a result of both these factors the meal imposes a less severe strain upon the absorptive capacity of the patient.

In our previous communication we produced evidence that the dumping syndrome is caused, in patients sensitive to a sudden fall in circulating volume, by an osmotic shift of fluid from the circulation into the lumen of the intestine. On the basis of the observations reported here we suggest that the essential factor in the production of the osmotic shift is a defect in carbohydrate metabolism. Following partial gastrectomy, glucose is presented to the intestine more rapidly than usual. Most patients react to this by an adaptation of glucose metabolism by which the glucose-tolerance curve remains normal, absorption proceeds rapidly, and there is only a small osmotic transfer of fluid into the intestine. In some patients this adaptation does not occur. In these patients the glucose-tolerance curve is of the lag type, glucose absorption is relatively slow, and a large osmotic shift of fluid occurs, which, by increasing the rate of gastric emptying, increases the osmotic load: thus a vicious circle is set up.

The observation that the administration of insulin can diminish the fall in plasma volume and modify the symptoms of the dumping syndrome has obvious therapeutic implications. A small number of patients are being treated by subcutaneous insulin, either once or twice a day before meals. It is as yet too early to reach firm conclusions, but preliminary results are encouraging, many of the patients showing not only subjective benefit, with lessening of distension and exhaustion, but also objective improvement as shown by cessation of diarrhoea and a gain in weight. Full results will be reported later.

Summary and Conclusions

Observations were made of (*a*) the changes in blood-sugar concentration, and (*b*) alterations in plasma volume following the oral administration of 175 ml. of 50% glucose to 26 patients who had undergone gastrectomy, and to one patient who had had a gastro-enterostomy. In these 27 patients the test was performed 34 times.

In patients with a large fall in plasma volume following the ingestion of hypertonic glucose, the rise in blood sugar was more pronounced and prolonged than in those with a small fall.

A direct linear correlation was found between the maximum fall in plasma volume caused by the hypertonic glucose and the rate at which the blood-sugar concentration rose in the first 10 minutes after the ingestion of the glucose.

In patients in whom the hypertonic glucose caused a large fall (>8%) in plasma volume, the administration of insulin so as to lower the blood-sugar concentration at the time of the ingestion of the glucose diminished this fall and also lessened or abolished the associated dumping symptoms.

Insulin was also shown to have a similar effect in diminishing the fall in plasma volume and abolishing dumping symptoms following a meal rich in carbohydrate.

The hypothesis is put forward that the essential factor in the production of the dumping syndrome is a defect of carbohydrate metabolism, as a result of which the glucose-tolerance curve is of the lag type and glucose absorption is relatively slow. This results in an increased osmotic transfer of fluid into the intestine, causing a large fall in plasma volume which, in those patients sensitive to such a fall, gives rise to the dumping syndrome.

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EFFECT OF PRETREATMENT WITH METHYLTHIOURACIL ON RESULTS OF ^{131}I THERAPY

BY

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Little is known about the fundamental biological changes produced in thyroid cells when they are irradiated by radioactive iodine, and still less about factors which modify these changes. It might be expected that thyroid tissue would become more sensitive to ionizing radiations after treatment with antithyroid drugs which increase both the vascularity of the gland (Thomas, 1945) and the number of mitoses in thyroid cells (Řeřábek and Řeřábek, 1947). Indeed, Williams *et al.* (1949) in an uncontrolled trial had the impression that patients pretreated with propylthiouracil required a lower dose of ^{131}I than untreated cases. Furthermore, Fraser *et al.* (1954) devised a procedure which involved pretreatment by methylthiouracil and thyroxine and which was said to give more consistent results than the standard methods of ^{131}I administration. On the other hand, Chapman and Maloof (1955) and Blomfield *et al.* (1959) observed no consistent difference in the response of those which had received no pretreatment. Werner (1955), however, states that methylthiouracil produces a radioresistant gland.

Since ^{131}I produces its effects relatively slowly it is sometimes necessary to control thyrotoxicosis with antithyroid drugs before treatment with the radioisotope. Moreover, many patients are referred for this form of treatment who have previously received courses of antithyroid drugs. We decided, therefore, to carry out a trial to see whether pretreatment with methylthiouracil influenced the results of ^{131}I therapy.

We decided to use a simple clinical method for the assessment of the dose of ^{131}I which we would use. This is similar to that described by Macgregor (1957), and we report our experience using this procedure. Our results confirm and extend his conclusions.

Material and Methods

One hundred and fifty patients in whom the diagnosis of thyrotoxicosis had been confirmed by the clinical index, described by Crooks *et al.* (1959), and by ^{131}I studies were considered on the criteria laid down by Blomfield *et al.* (1955) to be suitable for ^{131}I therapy.

Since the method of assessment of dosage is subjective and the prescribing physician might have altered his criteria during the three and a half years over which the observations were spread, certain precautions were taken in the design of the investigation. The doses of ^{131}I given to the different groups of patients were prescribed by the same physician (J. C.), and the observations on pretreated cases were controlled by those on untreated cases over the same time intervals. Four groups were studied.

Group 1 consisted of 28 patients who had received methylthiouracil for periods ranging from three months to one year. Administration of the drug ceased one week before treatment with ^{131}I. At this time all the subjects were either euthyroid or minimally thyrotoxic.

Group 2 consisted of 45 patients who had been treated with ^{131}I over the same period as Group 1, and who had never received an antithyroid drug.

When it became clear that methylthiouracil conferred some degree of radioresistance on the thyroid gland two further groups were studied.

Group 3 consisted of 21 patients previously treated with methylthiouracil in the same way as those in group 1 but in whom the dose estimated in the standard manner was arbitrarily increased by 25%.

Group 4 acted as the control to group 3. It included 56 patients who were not pretreated and whose dose was determined in the same way as that of patients in groups 1 and 2. They differed from group 2 only in the fact that they were treated contemporaneously with group 3.

All cases, with the exception of a few who were treated early in the course of the investigation, were given tracer doses of ^{131}I during the week before treatment in order to determine the 48-hour gland uptake of ^{131}I. In patients who had been receiving methylthiouracil the drug was stopped 48 hours before the tracer dose was administered.

Method of Dose Estimation

The basic principle of dose estimation used was that small doses were prescribed for patients with small glands and large doses for patients with large glands. It was decided from a review of the results of other workers that patients with impalpable glands would be given doses of 4–5 mc., those with minimal but definite diffuse enlargement of the gland 6–7 mc., and patients with larger glands doses from 7–25 mc. according to the size of the goitre. Many other factors besides gland size influenced the dose prescribed; for example, post-thyroidectomized patients were given 5–6 mc., unless the gland remnant was exceptionally large. Relatively high doses were given to patients with nodular glands, cardiac

failure, and uncontrolled diabetes mellitus, or whenever the risk of producing hypothyroidism was less than the need for a rapid remission of symptoms.

While each patient was being examined with a view to dose prescription the size of the gland was estimated in grammes, though the inaccuracies of this estimate are fully appreciated. This was done in order to obtain, *after each patient had been treated*, the dose which would have been given if the formula for dose prescription given by Blomfield *et al.* (1955) had been used. This formula is

$$\text{Dose in rads* per mc.} = \frac{805 \times \text{48-hour \% uptake of gland}}{\text{mass of gland (grammes)}}$$

These workers aimed to give 7,000 rads for diffusely enlarged glands, 5,000 to 7,000 rads for small post-operative recurrences, and 8,000 rads or more for large and multinodular glands.

Follow-up Procedure

All patients were seen at monthly intervals at the endocrine clinic until they had become euthyroid. The assessment was initially made on clinical grounds but was confirmed by a basal metabolic rate (B.M.R.) estimation. The necessity for retreatment was considered three to four months after the initial dose. Dose prescription in the case of retreatment was based on the same principles as those for the first treatment. Doubtful cases were left for a further two months, and if by that time the presence of toxicity was still in doubt they were readmitted to hospital for further detailed study before a final decision was made. After patients became euthyroid they were seen at intervals of two to six months as the circumstances warranted. Cases suspected of hypothyroidism on clinical grounds were further investigated by estimations of serum cholesterol and of the B.M.R. and by electrocardiography. If the hypothyroidism was mild no replacement therapy was given, because it is known that transitory hypothyroidism may occur after ^{131}I therapy. If the hypothyroidism persisted for three to four months and became more marked, then L-thyroxine sodium was prescribed. Hypothyroidism was thought to have been produced by ^{131}I therapy only if treatment with thyroxine was necessary.

The minimum period of follow-up was one year and the maximum three and a half years. Cure was considered to have taken place if the patient was euthyroid at 12 to 18 months.

Biological Half-life of the Therapeutic Dose

The biological half-life of ^{131}I was measured in 13 patients of group 1 and 16 patients of group 2. This measurement was obtained as follows. An uncollimated scintillation counter with 1 in. (2.5 cm.) of lead filtration was used in conjunction with an Ekco autoscaler. On the second day after the therapeutic dose of ^{131}I had been administered the counter was set up 12 in. (30 cm.) above the isthmus of the thyroid gland and the radio-activity counted for 100 seconds. The neck was then shielded with 2 in. (5 cm.) of lead and a background count made in order to obtain the net radioactivity from the gland in counts per 100 seconds. This procedure was repeated at intervals until the gland radioactivity had fallen by one-half. After these values had been corrected for physical decay they were plotted against time, using semi-logarithmic paper, and the biological half-life was accepted as the time taken for the radio-activity to fall to half of its original value.

Results

Table I shows the clinical result of ^{131}I therapy in glands of different types.

Group 1 (28 cases).—Of the 28 patients in this group, only 8 (28.6%) became euthyroid with one dose of ^{131}I, though cure was achieved by 18 months in 24 (86%). Two patients developed hypothyroidism and there were two failures. The mean number of doses given to this group was 2.35.

Group 2 (45 cases).—The incidence of nodular and post-operative glands in this group was similar to that of group 1. The one-dose cure rate was 75.5% and the increase over the comparable figure for group 1 (28.6%) was statistically significant. Two cases of this group developed hypothyroidism and there were three failures. The mean number of doses given was 1.5.

Group 3 (21 cases).—Ten cases (47.5%) of this group became euthyroid with one dose. Two cases became hypothyroid, and there were no failures. The mean number of doses given was 1.9.

Group 4 (56 cases).—Thirty-three patients (59%) of this group became euthyroid with one dose, and this one-dose cure rate, while higher, was not significantly

*One rad = 100 ergs per gramme of tissue.

TABLE I.—*Results of ^{131}I Therapy*

Group	Type of Gland	No. of Cases	Euthyroid				Myxoedema			Still Toxic at 18 Months
			% of Total	Total	One Dose	2 or More Doses	Total	One Dose	2 or More Doses	
1	Diffuse (including not palpable)	19	68	17	7	10	0	0	0	2
	Nodular	6	21	4	0	4	2	1	1	0
	Post-thyroidectomy	3	11	3	1	2	0	0	0	0
	Total	28	100	24 (86%)	8 (28·6%)	16 (57·4%)	2	1	1	2
2	Diffuse (including not palpable)	28	62	27	25	2	1	1	0	0
	Nodular	11	25	8	5	3	1	1	0	2
	Post-thyroidectomy	6	13	5	4	1	0	0	0	1
	Total	45	100	40 (89%)	34 (75·5%)	6 (13·5%)	2	2	0	3
3	Diffuse (including not palpable)	14	67	12	6	6	2	2	0	0
	Nodular	7	33	7	4	3	0	0	0	0
	Post-thyroidectomy	0	—	0	0	0	0	0	0	0
	Total	21	100	19 (90·5%)	10 (47·5%)	9 (43%)	2	2	0	0
4	Diffuse (including not palpable)	29	52	28	19	9	1	0	1	0
	Nodular	21	37·5	17	10	7	3	0	3	1
	Post-thyroidectomy	6	10·5	6	4	2	0	0	0	0
	Total	56	100	51 (91·5%)	33 (59%)	18 (32·5%)	4	0	4	1

TABLE II.—*Biological Half-lives of Therapeutic Doses of* ^{131}*I*

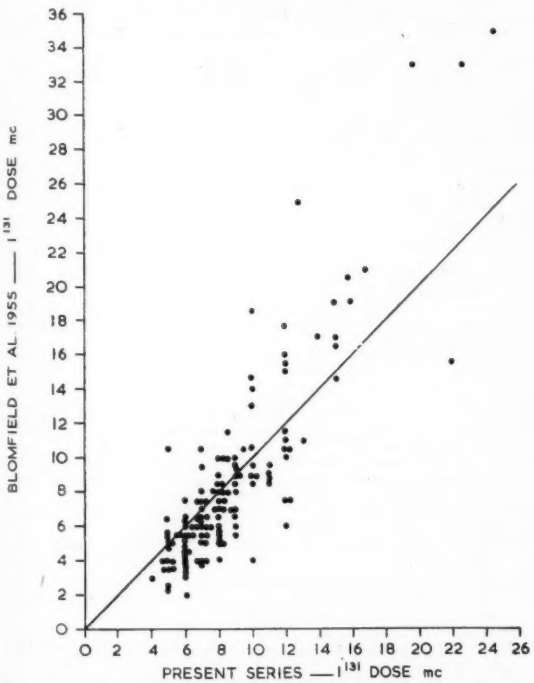
Cases Pretreated with Methylthiouracil (Days)		Cases with No Pretreatment (Days)	
9·4	9·0	17·8	12·4
13·2	11·3	17·0	10·0
13·0	14·8	20·0	15·6
8·0	11·0	4·7	4·0
5·0	20·0	7·0	7·0
8·5	6·0	14·4	23·0
14·0		7·4	15·2
		4·0	12·4
Mean = 11·0		Mean = 12·0	

different from that of group 3 (47.5%). Four patients of this group became hypothyroid, and there was one failure. The mean number of doses given was 1.6.

Biological Half-life of the Therapeutic Dose of ^{131}*I.*—The biological half-lives of ^{131}I of the 29 patients studied are shown in Table II. The mean biological half-life of the 13 patients of group 1 who had been pretreated with methylthiouracil was 11 days, and this was not significantly different from the comparable value of 12 days in the case of the 16 patients of group 2 who had received no pretreatment with an antithyroid drug.

Comparison of the Results of the Present Series with those of Blomfield et al. (1959)

In 101 cases of the present series not pretreated with methylthiouracil (groups 2 and 4) the one-dose cure rate was 68% and the incidence of hypothyroidism 6%. This was not significantly different from the one-dose cure rate (59%) and the incidence of hypothyroidism (12%) in 461 unpretreated cases reported by Blomfield *et al.* (1959). In the accompanying scattergram the doses used in the present series have been plotted against the doses which would have been used if the more elaborate method recommended by Blomfield *et al.* (1959) had been applied. It can be seen that in the lower-dose range there has been a tendency for the latter workers to give smaller doses, while in the higher-dose range larger doses have been given. This difference is not reflected in either the one-dose cure rates or the incidence of hypothyroidism in the two series.



Therapeutic doses of ^{131}I prescribed in the present series plotted against doses calculated from the formula of Blomfield *et al.* (1955). The oblique line has been drawn at 45 degrees to the ordinates.

Discussion

The results of radioactive iodine therapy in cases pretreated with methylthiouracil (group 1) showed a significantly lower one-dose cure rate than cases which had received no pretreatment (group 2). It can be seen from Table I that this finding cannot be accounted for by variations in gland types between the two groups. Furthermore, consistency of dosage prescription was obtained by the design of the observation which ensured that the same physician treated both groups during the same interval of time. Increasing the dose of ^{131}I in pretreated cases (group 3) raised the one-dose cure rate to that of an untreated control group (group 4). The findings could be explained if methylthiouracil pretreatment shortened the biological half-life of the therapy dose, but no significant difference was found between the mean biological half-lives of therapeutic doses of ^{131}I in a group of patients who had received the antithyroid drug before radioactive iodine therapy and in a group who had not. The difference between the pretreated and untreated groups could be due to a more patchy distribution of the therapeutic dose of radioactive iodine in the former, but there is no published evidence on this point.

The only other explanation which could account for the findings is that the methylthiouracil-treated gland is relatively radioresistant, and there is some experimental evidence to support this view. For instance, Dale (1947, 1952) and Dale *et al.* (1949) have demonstrated that thiourea protects carboxypeptidase, an enzyme in aqueous solution, against the effects of irradiation, and Limperos and Mosher (1950) have shown both *in vitro* and *in vivo* the same phenomenon in the case of nucleoproteins. The radioprotective effect of thiourea compounds has also been shown in bacteria (Forssberg, 1950) and in intact animals (Mole *et al.*, 1950; Lorenz *et al.*, 1952). Since there is some evidence that the diminished availability of intracellular oxygen produces radioresistance (Hollaender and Stapleton, 1953; Gray, 1954), the mechanism of the protective effect of methylthiouracil in the thyroid irradiated by ^{131}I may lie in the fact that it is a reducing agent. It is also of interest that other compounds containing sulphur or sulphydryl groups have a radioprotective action (Patt *et al.*, 1952; Rugh and Wang, 1953; Bacq, 1954; Gray, 1954). Rugh (1953) found that thiouracil gave protection to the thyroid cells of the Japanese fire salamander (*Triturus pyrrhogaster*) against irradiation by radioactive iodine for periods up to seven months following the cessation of administration of the drug. A similar effect in the human subject would explain why we observed relative radioresistance, though a week had elapsed between the last dose of the drug and the administration of ^{131}I.

This radioprotective action of methylthiouracil may explain the results obtained by Fraser *et al.* (1954). These workers pretreated patients receiving ^{131}I therapy with methylthiouracil and thyroxine. They subjected the thyroid to a much greater dose of radiation than Blomfield *et al.* (1955), but nevertheless recorded a smaller incidence of hypothyroidism.

The accurate determination of a single dose of radioactive iodine sufficient to produce cure of thyrotoxicosis presents the major practical difficulty in the application of this form of treatment. The majority of workers use techniques for estimating the therapeutic dose based on assumptions that the mass of the gland and the biological effect of ^{131}I can be accurately measured. It is generally recognized that the estimation of gland volume is inaccurate (Soley *et al.*, 1949 ; Loevinger, 1953 ; Kelly, 1954), and that the biological half-life of the therapeutic dose is difficult to predict from the turnover of a tracer dose (Skanse, 1948 ; Miller and Sheline, 1951 ; Freedberg *et al.*, 1952 ; Blomfield *et al.*, 1955). Though the uptake of the therapeutic dose of ^{131}I by the thyroid gland can be assessed with fair accuracy from the behaviour of a tracer dose (Keating *et al.*, 1949 ; Freedberg *et al.*, 1952), the distribution of the isotope in the gland has been shown to be very variable (Fitzgerald and Foote, 1949 ; Kelsey *et al.*, 1949), and especially so in nodular glands (Chapman and Maloof, 1955). The remaining factor which influences dose estimation is the sensitivity of the thyroid tissue to irradiation, and, though little is as yet known of the variability of this factor, there is evidence to suggest that considerable variation in gland radiosensitivity does occur (Myant and Pochin, 1955). Owing to these uncertainties it is not possible to estimate precisely the dose of radioactive iodine to give an optimum amount of irradiation.

Most published results in this field refer to groups of patients which include unspecified numbers of pretreated and untreated cases. Now that we have shown that pretreatment produces relative radioresistance, comparison with such series is impossible. Our results, however, in 101 untreated cases using a simple clinical dosage scheme compare favourably with those obtained in the unpretreated cases reported by Blomfield *et al.* (1959), who used an elaborate and quantitative predetermined dosage method. We agree with Macgregor's (1957) conclusion that precise methods of estimating the therapeutic dose of radioactive iodine offer no significant advantages.

It is of interest that when a simple clinical method of dose estimation is used the prescribing physician tends to be influenced in his decision by psychological factors. For instance, it can be seen (see Fig.) that the doses prescribed in the present investigation tended to be larger in the lower-dosage range and smaller in the higher-dosage range than those which would have been prescribed had the method recommended by Blomfield *et al.* (1955) been used. Thus when large doses have to be prescribed the physician using a purely clinical method tends to be unduly influenced by the dangers of potential hypothyroidism, whereas in the low-dose range he hopes to achieve cure with one dose and therefore is less inhibited. There is no statistical difference between the one-dose cure rates, probably because large doses are given relatively rarely and the percentage differences with larger doses are much less than with smaller ones. Halnan (1959) has pointed out that, because one needs to leave intact a constant mass of thyroid tissue and not to destroy a constant proportion of the gland, small glands will need a less-than-expected radiation dosage and large glands a higher dosage.

The present investigation has clearly confirmed that a simple technique without complicated measurements can be used provided simple rules are observed. This procedure achieves the maximum economy in both physician's and patient's time.

Summary

The one-dose cure rate in 28 patients who had been treated with methylthiouracil until the week before ^{131}I therapy (28.6%) was significantly lower than that of 45 patients who had had no previous drug therapy (75.5%). This difference could not be accounted for by differences in gland types or in the biological half-lives of the therapy doses of ^{131}I.

The dose of ^{131}I was increased by 25% in a further 21 patients pretreated with methylthiouracil, and the one-dose cure rate in this group (47.5%) was not significantly different from the one-dose cure rate in 56 patients who had received no pretreatment (59%).

It is concluded that pretreatment with methylthiouracil until one week before ^{131}I is given renders the gland relatively radioresistant.

A simple clinical method of dose prescription was used in this study, and the results obtained in 101 cases not pretreated with antithyroid drugs and observed for a minimum period of one year are as satisfactory as those reported in an investigation which aimed at delivering a predetermined amount of irradiation to the thyroid gland.

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SUCCESSFUL CARDIAC MASSAGE FOR CARDIAC ARREST FOLLOWING CORONARY THROMBOSIS

BY

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Cardiac massage is commonly and successfully performed for cardiac arrest during and immediately after anaesthesia. In the following case cardiac arrest was successfully performed in a hospital ward bed on a patient who developed cardiac arrest following a coronary thrombosis. A summary of the procedure is given and several features of interest are discussed.

Case Report

On the late afternoon of March 24, 1959, a labourer aged 54 was admitted to hospital with a history of having suddenly experienced, three hours previously, a severe upper retrosternal pain with radiations across the upper chest, down the left arm, and into the neck. He described it as the worst pain he had ever had. It was still present on admission, but had been eased slightly by ¼ gr. (16 mg.) of morphine given two hours after the onset by the patient's own doctor.

For the previous 14 months he had been having episodes of high retrosternal pain, radiating down the left arm, lasting up to 15 minutes, and bearing no relation to food, posture, exertion, or breathing. No definite diagnosis had been made concerning this pain.

On admission he was shocked, the skin being cold and moist, with some slight cyanosis of the lips. He was not dyspnoeic. All pulses were palpable but weak. His blood-pressure was 110/60, pulse 64 and regular. The heart sounds were normal. All other systems were normal. A clinical diagnosis of coronary thrombosis was made and 12,500 units of heparin were given intramuscularly.

Fifteen minutes after the physical examination was completed he collapsed. Respirations ceased, pulses were not palpable, no heart sounds were audible, and corneal reflexes were absent. Artificial respiration and oxygen under pressure via a face-mask was given for a period of three minutes, at the end of which his condition was unchanged and he was thought to be dead.

On the ward bed, without aseptic precautions, thoracotomy was performed through the left sixth intercostal space and the ribs were forced apart manually. No bleeding occurred. The heart was palpably and visibly immobile and was distended. The pericardium was not opened. Cardiac massage was started, the heart being compressed between the hand and the anterior chest wall. After five minutes there was still no spontaneous movement of the myocardium, so massage was continued.

Meanwhile an endotracheal tube had been passed by a member of the resident staff and the patient was adequately oxygenated under positive pressure from a Boyle machine. There was still no spontaneous respiration at this point. Towards the end of the 10th minute of massage, small localized movements could be felt in the left ventricle. The frequency and site of these increased until by the 15th minute since opening the chest both ventricles were fibrillating. By the 19th minute 5 ml. of 2% procaine hydrochloride was injected intravenously in the arm and massage of the fibrillating ventricle continued. Within 30 seconds of the injection normal heart contractions could be felt. A further 10 ml. of 2% procaine was given, by which time the fibrillation had stopped and the heart was beating normally. Spontaneous respirations had begun.

For a further five minutes normal heart action was observed through the chest wall, a blood-pressure of 110/70 and a pulse of 100 being recorded. During this period an intravenous drip of dextrose–saline containing 50 ml. of 1% procaine, 0.5 g. of oxytetracycline, and 4 ml. of "levophed" was set up. An underwater seal drain was fixed through a stab incision in the left lower chest and the chest closed with a continuous suture.

Half an hour later the patient's blood-pressure was 140/70, pulse 98 and regular, colour good, and respirations 22. He was very restless. *The endotracheal tube was removed* and he was given 20 ml. of paraldehyde intramuscularly. Further progress during the night was uneventful. After eight hours the intravenous drip was discontinued.

Next morning, 13 hours after the operation, his condition remained satisfactory. He was awake, somewhat drowsy, and complained of pain in the region of the wound. Mentally he appeared normal. He was able to take fluids by mouth. That same morning an electrocardiogram (Fig. 1) showed a posterior infarction.

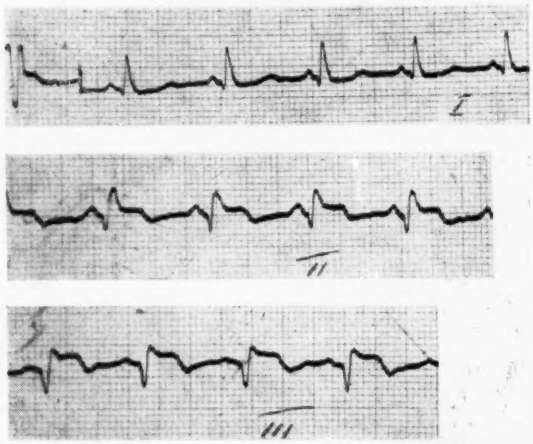

FIG. 1.—Standard leads taken the day after operation.

Except for a small area of sepsis at the top end of his wound, the post-operative course was uneventful. Heparin, 12,500 units b.d., was changed to phenindione in the usual way. He also received 1 mega unit of penicillin b.d. for eight days, and tetracycline 250 mg. q.i.d. for 10 days.

The chest drain was removed and the suture was taken out on the 10th day. An electrocardiogram taken on the 15th day is shown (Fig. 2).

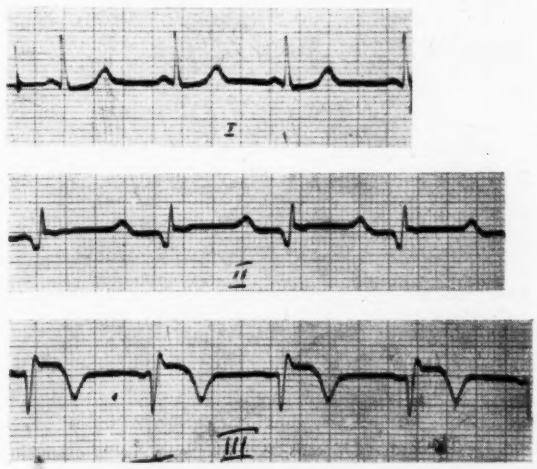

FIG. 2.—Standard leads taken 15 days after operation.

X-ray examination of chest on April 27 showed that the cardiac shadow was within normal limits. There were slight basal congestive changes only and no gross pulmonary lesion was noted.

Four weeks after admission the patient was allowed out of bed, and two weeks later he was walking about the ward and appeared normal in every way. Neither we nor his relatives could detect any mental abnormality. He showed no residual neurological signs of cerebral anoxic damage (Fig. 3) After seven weeks he was discharged home.

When seen on July 23, he was well and his exercise tolerance was quite fair. He complained of some tenderness at the wound site. Clinically his chest was clear. An electrocardiogram (Fig. 4) was done on that date. He was told that there was no reason why he should not be able to take a light job in two months' time.

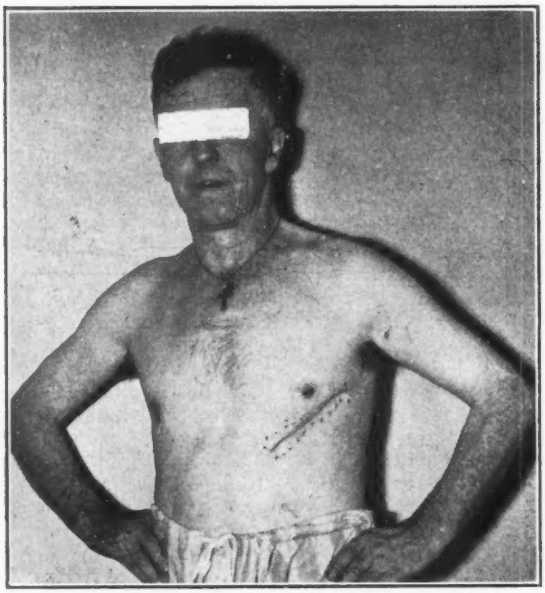

FIG. 3.—Photograph taken six weeks after operation.

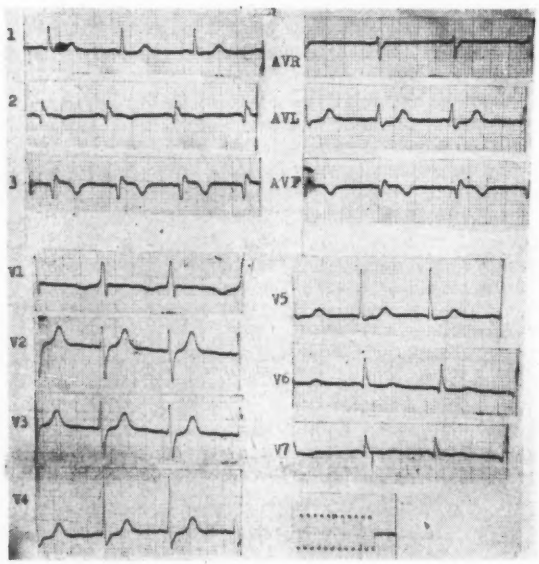

FIG. 4.—Standard and V leads taken four months after operation.

Discussion

So far as can be ascertained there is no record in this country of complete cardiac asystole from coronary thrombosis being resuscitated with uneventful recovery and well-being four months later. Nor is there any record of ventricular fibrillation following asystole being arrested by procaine hydrochloride without the use of electrical defibrillation.

Several other successful cases of resuscitation following coronary thrombosis have been described (Beck, Weckesser, and Barry, 1956). The usual finding at thoracotomy, however, was ventricular fibrillation, normal rhythm being restored by cardiac massage and electrical defibrillation. Resuscitation in cases where there has been complete cardiac standstill is less common (Hannon, Brainard and Flom, 1957) and prolonged survival rare.

Consideration of the history and clinical condition of this patient undoubtedly shows that he had a coronary occlusion on the day of admission. Cases are described where cardiac massage has been performed for cardiac arrest due to conditions other than coronary artery disease or thrombosis, and electrocardiographic changes remotely suggestive of coronary thrombosis have not been found (Celio, 1956). Therefore, though electrocardiography was delayed 24 hours, we can accept the abnormalities with the history as being diagnostic of coronary occlusion and nothing else.

Cardiac arrest is a death-dealing complication of coronary artery disease, and a large proportion (up to 90%) of these deaths are due to disturbances of conductivity or "electrical instability" rather than the primary failure of the heart muscle. In the former group it is estimated that about one-third of the victims die without damage to heart muscle, the other two-thirds having muscle damage but not to such an extent as to be incompatible with normal heart action (Beck *et al.*, 1956). Therefore all the heart needs is to be given another chance to beat.

The action of procaine in reducing irritability of the myocardium is well known, and in this case it appeared to work satisfactorily. Other reports of its use in experimental animal ventricular fibrillation are conflicting (Dodds and Ashmore, 1959). However, it would appear to be the best drug for reducing "irritability" of the myocardium, and if one can accept the fact that a large proportion of deaths from coronary thrombosis are due to conductive or electrical instability within the myocardium, it might be reasonable to consider the prophylactic use of drugs of the procaine type in suitable cases of coronary artery disease, including thrombosis.

The whole of the procedure described was done in the ward of a small hospital containing 80 general beds. There is no specialized cardiac unit. The versatility shown and the speed at which equipment and drugs were obtained, throw great credit on the nursing staff.

Resuscitation from cardiac arrest following coronary thrombosis can be done successfully with a minimum of equipment. The onus of carrying out this procedure will almost certainly fall on junior hospital staff. The

procedure is not difficult. There is nothing to lose and a life to gain. Time is the important factor. Cerebral anoxia of 3½ to 5 minutes can produce irreversible anoxic damage to the brain. A defibrillating apparatus may or may not be to hand. Electrocardiograms take time, and the decision whether there is ventricular fibrillation or asystole is not an easy one. It has been suggested that where there is doubt an incision should be made in the chest wall. If it bleeds the patient will most certainly be fibrillating. Absence of bleeding indicates asystole. With the former one may have time to wait and try the effects of electrical or chemical defibrillation.

On August 20, five months after the incident, the patient was alive and well. There had been no recurrence of his retrosternal pain.

Summary

This is a case where a patient collapsed for a period of approximately 3 minutes, shortly after admission to hospital with a coronary thrombosis. Simple measures of resuscitation were attempted without effect, and he was presumed to be dead. Through a left sixth intercostal incision the asystolic heart was massaged manually for 10 minutes. At the end of this period the ventricles began to fibrillate spontaneously: this was converted to normal rhythms by an intravenous injection of procaine 2%.

The patient made an uneventful recovery without evidence of cerebral anoxic damage, and was alive and well at the time of writing, nine months later.

A short discussion of the problems and management of cardiac arrest following coronary thrombosis is given.

I thank Dr. B. F. Brearley for allowing me to publish this case, Dr. D. M. Anderson for his helpful criticism and suggestions in preparing the script, and Dr. E. Milne for his rapid intubation of the patient and assistance during the procedure.

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During this twenty-first anniversary year, the National Marriage Guidance Council (*Annual Report, 1959–60*) says that 12,000 couples were helped in marriage difficulties; over 1,000 counsellors have now been accepted, and are either trained or in course of training; about 45 marriage guidance councils provided group preparation for marriage for engaged couples; and about 100,000 booklets published by the council were sold during the year under review. The council are buying a long lease of 58, Queen Anne Street, the present headquarters of the Royal College of Obstetricians and Gynaecologists, and finding the money for this, as well as for higher salary scales, "presents a formidable task." The council welcome the increase in their Government grant from £10,000 a year to £15,000 from April 1 this year, but they add: "The Government would have to give us similar increases every year for 197 years before their grant equalled the present cost to public funds of legal aid for divorce."

TWO EPISODES OF CARDIAC ARREST IN ONE WEEK

FULL RECOVERY AFTER CARDIAC MASSAGE

BY

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Complete recovery from one episode of cardiac arrest is no longer unusual. Most surgeons and anaesthetists have had personal experience of the treatment of this emergency, and the pooling of their experience in isolated cases has led to a gradual understanding of the causes, prevention, and management of cardiac arrest. Apart from cardiac surgeons, few have had the opportunity to study and compare the causes of repeated episodes of cardiac arrest in one patient. This paper records the history of a severely burned child whose heart stopped during the induction of general anaesthesia for skin-grafting operations on two separate occasions. This case closely resembles one described by Finer and Nylen (1959) from Sweden. In both cases cardiac arrest occurred twice within a week during the induction of endotracheal anaesthesia, and in both another general anaesthetic without intubation had been given successfully the day before the second episode of arrest. While in the Swedish case the patient recovered from the first arrest without massage, in the present case cardiac massage was required on each occasion.

Case History

A girl aged 6 years was admitted to the Footscray and District Hospital on May 28, 1957, with severe burns from the ignition of clothes soaked with kerosene. There was full-thickness skin-loss from the whole of the lower half of the body from the level of the iliac crests to the ankles, except for the anus and the labia majora. The circumferential burns were treated by the closed-dressing method combined with frequent changes of position to try to prevent additional loss of tissue from pressure necrosis. Despite unavoidable faecal and urinary contamination the burns remained reasonably clean, but the child ran a hectic temperature and required frequent small blood transfusions and continuous intragastric feeding of high-protein fluids during the night to prevent rapid deterioration of her condition.

The dressings were changed six times under general anaesthesia between June 4 and 25, inclusive, without any anxiety. Then, on June 26, under endotracheal anaesthesia, split skin was cut from both arms and from the back and successfully applied as "postage stamp" grafts to the whole of the right leg and the back of the left leg. When dressed under general anaesthesia on June 30, all grafts were seen to have taken. However, the child still had a high temperature and was losing weight rapidly. It was decided that skin-grafting should proceed at once before her condition became critical.

First Cardiac Arrest

On July 2 further grafting was proposed. Immediately before operation the child's temperature was 99.4° F. (37.4° C.), pulse rate 140/min., and respiration rate 28/min.

The haemoglobin was 13.4 g./100 ml. Pre-operative medication of "omnopon," 10 mg., and hyoscine, 0.2 mg., was given subcutaneously at 4.15 p.m.

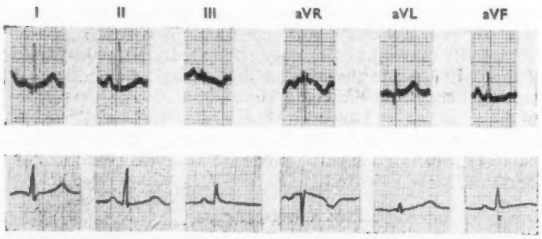
In the anaesthetic room, at 5.30 p.m., a sleep dose of 0.12 g. of thiopentone was injected intravenously followed by 50 mg. of suxamethonium chloride. After oxygen inflation the larynx was sprayed with 2% amethocaine from a Macintosh laryngeal spray and intubated with a No. 4 non-cuffed endotracheal tube, as it was proposed to operate with the patient prone. Nitrous oxide, 5 l./min., with oxygen, 2 l./min., was then administered through the semi-open circuit of a Boyle anaesthetic machine and minimal trichlorethylene slowly added. (The plunger of the trichlorethylene bottle was fully withdrawn and the lever moved to second division.) During this time the patient's colour and pulse had remained perfectly satisfactory, and she was then transported to the adjoining theatre.

At 5.33 p.m., while she was still on the trolley prior to transfer to the operating-theatre table, the sudden onset of cyanosis was noticed. There had been no change in the anaesthetic mixture, but manual inflation had still been necessary, as the effects of the suxamethonium had not yet worn off. The nitrous oxide and trichlorethylene were stopped at once and manual inflation was continued with oxygen. The pulse was weak and irregular. A check of the anaesthetic machine and position of the endotracheal tube failed to show anything wrong, but the pulse continued to become weaker over the next minute, despite the adoption of the Trendelenburg position, and carotid pulsation ceased at 5.35 p.m.

An incision through the fourth left intercostal space was at once made and cardiac massage begun at approximately 70 beats a minute. The incision was enlarged by dividing the third and fourth costal cartilages and the pericardium was opened. A small straw-coloured pericardial effusion was present. Massage improved the tone of the heart, which was dilated and fibrillating, but regular rhythm did not return. No drugs were given at any time. The pupils, which had been fully dilated, returned to a mid-dilated position, and bleeding started from the divided internal mammary artery. The lungs were inflated manually with oxygen. After some minutes occasional diaphragmatic contractions were felt, and at 5.37 p.m. weak and intermittent ventricular contractions occurred momentarily. Spontaneous respiration returned before the resumption of normal cardiac rhythm, and at the same time the child began to stir and had to be restrained gently. Strong, regular spontaneous beats did not return until 5.48 p.m., just as a defibrillator urgently summoned from another hospital arrived. The chest was closed with underwater seal drainage and the child was returned to the ward. No grafting was undertaken. An electrocardiogram taken after the chest had been closed showed changes suggestive of posterior myocardial ischaemia (see Fig.).

Massage had been maintained during a period of approximately 12 minutes of cardiac arrest.

Over the next few days the dressings became offensive, and it became obvious that something further should be done soon, as her general condition was deteriorating rapidly, apparently because of infection of the burns rather than because of chest infection. Her colour and respiration rate were unaltered and there were no moist sounds. *X*-ray films showed that the left lung remained fully expanded, but there was segmental collapse of part of the right middle lobe, and a small indefinite opacity over the front of the heart which after a few days was identified as a small loculated collection of fluid at the left cardiac border. The thoracotomy wound did not suppurate. On the fourth day (July 6) a dressing of the burns, preparatory to further grafting, was carried out under very light nitrous-oxide-and-oxygen anaesthesia with minimal added ether, and administered by a face-mask. Premedication was with hyoscine, 0.2 mg., given subcutaneously. This was quite uneventful, though it involved several changes of posture and lasted half an hour. After some discussion on the merits of local and general anaesthesia, and encouraged by the success of the previous anaesthetic, it was decided to proceed with grafting of the remaining burns under general anaesthesia on July 7.



Above, electrocardiogram taken on July 2, 1957, showed a heart rate of 140 beats a minute and T inversion in lead III suggestive of posterior myocardial ischaemia. Below, electrocardiogram taken on November 6, 1958, showed a rate of 75 beats a minute; the graph was within normal limits.

The child's temperature was 100.2° F. (37.9° C.), pulse rate 132, and respiration rate 28. Urinary output was good. Respiration was noisy because of mucus in the main bronchi, but the alveoli were dry. At 9.30 a.m. hyoscine, 0.3 mg., was again given.

Second Cardiac Arrest

Anaesthesia was begun at 11.20 a.m., and on this occasion auscultation of the heart was continuous throughout induction. Nitrous oxide and oxygen, at the rate of 6 and 2 l./min. respectively, were given by a face-mask until the child was asleep. Then 40 mg. of suxamethonium chloride was injected intravenously and the lungs were inflated with oxygen. A No. 4 plain endotracheal tube was passed with ease, and inflation continued with oxygen. *Immediately the tube passed the larynx* the heart-beats slowed and became irregular, and the heart-sounds became progressively fainter over approximately 20 seconds and ceased completely at 11.23 a.m. The recent chest wound was immediately reopened and cardiac massage begun. Between the chest wound and the front of the heart was a collection of about 75 ml. of pus, which was spread around the pleural cavity as the massage continued. Once again the left ventricle was dilated and fibrillating; but gradually it regained its tone after being emptied by massage. No obvious bruising from the previous massage of the heart was seen. Adequate circulation was maintained and a pulse could be felt in the neck. Diaphragmatic contractions began and the child started to move, and eventually the arms had to be restrained to prevent any interference with the massage. However, she did not regain consciousness to a degree requiring the addition of an anaesthetic to the oxygen being given, prior to the resumption of the heart-beat. An arterial transfusion was being inserted when spontaneous rhythm returned at 11.50 a.m., again without the use of a defibrillator, which had to come from a neighbouring hospital.

Arrest had persisted from 11.23 a.m. till 11.50 a.m., a period of 27 minutes.

A swab was taken from the pleural cavity for culture and the chest wound was then closed with through-and-through sutures, making it as airtight as possible. As soon as the chest was closed the child awoke and asked for a drink. Hopes of having avoided cerebral damage were raised when she was handed a lemon drink and she said, "I want orange!"

On return to the ward she was nursed in an oxygen tent. Efforts were made to encourage coughing, the most effective being a change in position, but turning and postural drainage were not well tolerated because of pain. She spent most of the time lying prone with the chest and legs supported by "dunlopillo" cushions. Intramuscular tetracycline was given prophylactically while the results of pleural and sputum cultures were awaited.

Chest *x*-ray films on the day after the second cardiac arrest showed only a small left apical pneumothorax which did not move with change in posture. Considerable pleural fluid was present, but the lung was well expanded. A good colour was maintained when the patient was out of the oxygen tent, and she was bright and co-operative. The following day the left lung base was much clearer, and at the apex there was a localized collection of fluid and air which began to drain through the suppurating chest wound on July 10. The localization of this collection remained intact, and at no time was there a sucking pneumothorax nor general empyema. Furthermore, the drainage of the collection through the wound seemed quite adequate. The pleural and sputum cultures grew *Staphylococcus pyogenes* sensitive only to chloramphenicol, but this was withheld until July 12, when a segmental collapse of the right upper lobe extended into a complete upper-lobe collapse. Over the succeeding weeks the chest wound ceased draining and the empyema cleared completely. However, the collapse of the right upper lobe persisted, and it was decided not to risk bronchoscopy and the possible induction of another cardiac arrest. After some weeks the collapse slowly cleared, and by November 18 the chest was normal.

After the second cardiac arrest no further general anaesthesia during this illness was considered. Hypnosis was attempted on three occasions by a consultant psychiatrist, but the child was too active and anxious for it to be successful. Four days after the second cardiac arrest homografts were applied in the ward to provide a substantial temporary coverage of the large granulating wounds. The only sedation used was methylpentynol 16 ml. Dressings were continued twice weekly under a variety of sedatives. By August 27 most of the homografts had been rejected and the child's general condition had improved enough to allow further autografting. Between September 1 and October 19 the remaining granulating area was grafted in three stages, using local analgesia of ½% lignocaine and hyaluronidase.

No dressings were required after November 20, by which time the child was walking without assistance and joint movements of the legs were improving with active use. There was no oedema of the legs after walking, so that crêpe bandage support was discarded. When discharged from hospital on November 24 the child could stand upright with only slight hip-flexion due to scar contracture in both groins. The knees were straight. Simple tests indicated that her mental capacity was unimpaired. Three months later she had put on weight and looked a normal child. She was able to keep up with other children and ride a bicycle without respiratory distress.

She was last seen on November 6, 1958, 16 months after admission, on return from a visit to Europe. The grafted areas had remained intact and allowed full movements of all joints. There was no oedema of the ankles. She was able to take part in sports, and there was no evidence of a diminished cardiac reserve. Her parents indicated that there was no intellectual impairment. An electrocardiogram at this time (see Fig.) was within normal limits and her chest was normal.

Discussion

After the first cardiac arrest the agents and methods used prior to its occurrence were reviewed as possible responsible factors.

Thiopentone.—Serious cardiovascular effects from this drug are notorious, and it has been compared unfavourably with chloroform (Harris, 1951). It appeared unlikely to be responsible for this case of arrest, as a minimal amount (0.12 g.) had been administered very slowly just until sleep had been produced and the eyelash reflex abolished. The arrest did not take place until five minutes later.

Suxamethonium Chloride.—There was no evidence at the time to suggest that this widely used drug could cause cardiac arrest. Since then, however, Leigh, McCoy, Belton, and Lewis (1957) have reported bradycardia following the administration of suxamethonium, and have suggested its use could lead to cardiac arrest. Bullough (1959) has reported cases of cardiac arrest when an intermittent injection technique has been used.

Trichlorethylene.—Norris and Stuart (1957) reported seven cases of cardiac arrest during trichlorethylene anaesthesia, two of which occurred in children immediately it was added to the nitrous oxide and oxygen mixture during induction. The effect of irritant vapours in producing pulmo-cardiac reflexes which are enhanced by manual control of respiration has been stressed by Johnstone (1951). In spite of the fact that it had been administered previously without incident to this patient, it was felt that trichlorethylene must remain suspect in this instance.

Amethocaine Hydrochloride.—The toxic effects of this local anaesthetic on the cardiovascular system include bradycardia, feeble pulse, and cardiac failure. Moreover, signs of toxicity are more common after topical analgesia of the upper air passages than after local infiltration, as absorption from the lung is almost as rapid as intravenous injection. Though 2% amethocaine was in common use for topical analgesia of the cords many authorities consider 1% preferable. Apart from the question of individual susceptibility there seemed to be a strong possibility that the dose given might have been too much for this frail sick child. The time interval of three to four minutes before the arrest would also fit in with the expected rate of absorption of the drug. Though the multiple anaesthetics given to the child previously had included thiopentone, suxamethonium, and trichlorethylene, and tracheal intubation, this was the first instance in which amethocaine had been used. It appeared highly probable that this agent could have contributed to the arrest.

Vago-vagal Reflexes from Intubation

At the time this possibility was regarded as unlikely because of the long time interval between intubation and arrest, at least three minutes. Previous intubation had been without incident, and on this occasion there was the additional protective action of topical analgesia, though this was not necessarily complete at the time of intubation.

Despite the occurrence of one cardiac arrest, the child's age, her extreme distress, and the extent of the procedures to be undertaken made it necessary that another general anaesthetic be given. It was essential to reduce loss of blood and exposure to a minimum. If the child's co-operation was to be obtained using local analgesia, the heavy additional sedation required might have been more depressing to respiration than light general anaesthesia.

It was thought that a recurrence of the cardiac arrest might well be prevented by avoiding amethocaine, trichlorethylene, and thiopentone in any further anaesthetics. The successful administration of nitrous oxide, oxygen, and minimal ether on July 6, 1957, confirmed this view and encouraged the undertaking of the third anaesthetic on July 7, when it was proposed to follow the same technique except for the administration of the small dose of suxamethonium to make

intubation possible. Intubation was required as the child was to be turned face downwards during the operation.

During induction before the second arrest a stethoscope was placed on the praecordium and the heart was heard to slow, become irregular and faint, and then stop, the sequence beginning immediately the tube was inserted. It seems certain that arrest resulted from vagal stimulation initiated in the larynx. Stephenson, Reid, and Hinton (1953), in a review of 1,200 collected cases of cardiac arrest, stated that a vago-vagal reflex was the likely responsible agent in 156 out of 624 cases. About half of these 156 cases were due to manipulation of an endotracheal tube. Milstein (1956) recalled that during intubation the patient was often anoxic, and this might be a more important factor than vagal stimulation; however, in this instance intubation was easy and rapid in a well-oxygenated patient.

In Finer and Nylen's case cardiac arrest followed intubation on both occasions. The first anaesthetic had reached the stage of connecting the nitrous oxide and oxygen supply to the tube when arrest was noted. "Narkotal" (an ultra-short-acting barbiturate), pethidine, and suxamethonium had been used during induction. The induction before the second arrest in their case consisted of chlorpromazine, pethidine, narkotal, and suxamethonium followed by an unnamed analgesic spray. After intubation the patient was pink, and then over the next minute the pulse became increasingly rapid until it stopped. The heart was in asystole when massage began, and it rapidly resumed a normal rhythm. Finer and Nylen's conclusion was that direct laryngeal stimulation was the causative factor on both occasions. They, too, concluded that arrest had not occurred during another anaesthetic given between the two episodes of cardiac arrest because the patient was not intubated on that occasion. It is of interest that in their case the heart was observed to increase its rate, become uncountable, and then stop in asystole, while in our patient the heart rate slowed and became faint and irregular before arrest, which is more in keeping with vagal stimulation.

Finer and Nylen also discuss why cardiac arrest did not take place following three earlier anaesthetics with intubation, and suggest that the patient's fears may have passed a critical point before the fourth anaesthetic. There would seem to be little positive evidence for that assumption in their case and none in ours. We offer as a more likely explanation the gradual development of a toxic myocarditis secondary to the infected burns, in our case suggested by the tachycardia and the pericardial effusion. This could render the cardiac muscle more irritable and more susceptible to viscero-cardiac reflexes. Reid and Brace (1940) have reported that a considerable proportion of patients show electrocardiographic changes during intubation, and they suggest that these effects may be more significant in patients with structurally altered hearts.

It is possible that the choice of hyoscine rather than atropine as premedication facilitated the development of cardiac arrest from vagal stimulation. Hyoscine was chosen not only because of its sedative action, but because its administration would avoid the additional tachycardia expected with atropine. Though Goodman and Gilman (1955) state that 2 mg. of atropine is required to prevent the effects of vagal stimulation on the heart, it is probable that lesser amounts may produce a proportional degree of protection. It is of interest that atropine was not used in Finer and Nylen's case.

Experimental evidence suggests that ventricular fibrillation is unlikely to revert to normal rhythm without electrical defibrillation (Wégria, Frank, Wang, Misrahy, Miller, and Kornfeld, 1953). Our findings confirm those of Lampson, Schaeffer, and Lincoln (1948) that reversion can occur with cardiac massage alone, but we agree that a defibrillator should be used if it is available.

Conclusions

Though the cause of the first cardiac arrest in this case is not clear, the second was undoubtedly due to vagal stimulation induced by intubation. The risk of cardiac arrest from intubation of a normal patient properly induced is insignificant, but there is no doubt that intubation becomes an increasing risk in any patient with severe toxaemia from infected burns. The metabolic disturbance apparently potentiates the response to harmful viscero-cardiac reflexes, and so unnecessary vagal stimulation should be avoided in these cases. If intubation is essential we suggest that the administration of atropine might limit the effect of these vagal reflexes.

Summary

The history is reported of a child in whom cardiac massage was performed twice in one week with full recovery. Arrest occurred on each occasion during the induction of endotracheal anaesthesia prior to skin-grafting for extensive burns.

The possible precipitating factors are discussed, and it is concluded that the most likely cause was vagal stimulation during intubation.

This case is compared with a remarkably similar case of double cardiac arrest occurring during the treatment of burns recently reported by Finer and Nylen.

Study of both cases suggests that the severely burned patient becomes increasingly prone to cardiac arrest from vagal stimulation.

It is suggested that intubation be avoided in these patients, or, if it is essential, additional atropine be given to reduce vagal activity.

We thank Mr. Ian McConchie, Dr. Howard Whitaker, and Dr. Margaret McLelland for their help and advice in the management of this child at a time when her condition was critical. We are grateful to the Dunlop Rubber Company for supplying special dunlopillo mattresses, and to Calmic Pty. Ltd., for supplying "polybactrin." Finally, our thanks go to Dr. Ralph Howard and to Sister Eardly, of the children's ward, Footscray and District Hospital, for their constant care and attention to the child.

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CHEMOTHERAPEUTIC PITFALLS IN THE TREATMENT OF TUBERCULOSIS

BY

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"I find the medicine worse than the malady."
Francis Beaumont and John Fletcher,
The Lovers' Progress, III, ii.

One of the greatest disasters that can befall a tuberculous patient is that his organisms should become resistant to two or more of the standard anti-tuberculosis drugs, thereby denying him the most effective chemotherapy. Thus for those treating tuberculosis, avoidance of drug resistance has become a central theme of their work. Two known facts are of particular relevance to this problem. Anti-tuberculosis drugs employed *singly*, even in adequate dosage, lead to resistance when given for any length of time (Medical Research Council, 1950, 1952). The classical trials carried out by the Medical Research Council (1950, 1952, 1955) have also shown that certain *dual-drug* dosage schedules are fully acceptable as regards both efficacy and avoidance of resistance, provided the organisms are fully sensitive before the start of treatment. What is more, if such treatment is maintained for a sufficient period, up to 100% of sputum conversions can be expected (Middlebrook, 1956; Crofton, 1957). Thus it would seem that little difficulty should arise in the treatment of tuberculosis and that the disease could be managed easily by practitioners following rules based upon this knowledge. But one of the most difficult and not uncommon tasks facing the chest physician to-day is managing the patient who is found to harbour resistant organisms and who therefore does not respond to standard therapy. Misapplication of basic rules must thus be occurring.

In an effort to establish this, and more fully to understand the various causes of the emergence of resistant organisms, the clinical records of patients harbouring such organisms have been reviewed. To enable any conclusions to be drawn from these records it was necessary to assume certain basic "correct" methods of drug treatment with which comparison of actual treatments could be made. The M.R.C. schemes mentioned above were accepted for this purpose, and in this article other schedules are termed "faulty."

Another factor, already suspected as a cause of drug resistance, must be recognized when drawing conclusions from such records: the possibility that patients may not be consuming their orally prescribed medicaments. Thus if this occurs during the established administration of one drug the patient will receive this drug alone and strains of *Mycobacterium tuberculosis* resistant to it are likely to appear. It is reasonable to infer, conversely, that if correct dual therapy has been prescribed for a patient with drug-sensitive organisms and if resistance develops to a drug known to have been taken, then it is almost certain that the other drug was omitted. This reasoning has been followed in the present paper.

Finally, unless there is knowledge of the pretreatment drug-sensitivity pattern of the organisms there must be some uncertainty about any conclusions drawn. Particularly does this become significant when it is realized that some 5% of newly diagnosed untreated sufferers harbour resistant bacilli, presumably contracted from other maltreated patients (Fox *et al.*, 1957).

Method

With the foregoing points in view a careful examination was made of the full clinical records, still held at the Hammersmith Chest Clinic, of 32 patients with initially sensitive organisms and with resistance reported to one or more drugs. This group is selected in that, of a total of 51 patients with resistant organisms, 19 had been transferred elsewhere and were not available.

Most of the drug-sensitivity tests were carried out on Löwenstein–Jensen media slopes by the methods used at the Tuberculosis Chemotherapy Centre, Madras (1959). It is the practice in the case of streptomycin and sodium para-aminosalicylate (P.A.S.) to report results as resistance ratios (R.R.) because of variations in behaviour of the standard strain used for comparison (H37rV). Growth in relation to concentrations of isoniazid is not so varied, and results in terms of the absolute drug concentrations have been used. An organism is reported sensitive (S) to streptomycin or P.A.S. if the R.R. is below 4 and to isoniazid if there are less than 20 colonies growing on media containing 0.2 μg./ml. of isoniazid. Doubt is expressed ($\pm$) with an R.R. of 4 or if 20 or more colonies grow on 0.2 μg./ml. of isoniazid but not on higher concentrations. Definite resistance is reported ($+$) with an R.R. of 8 or more, or significant growth on 1 μg./ml. In this study R.R.s of 32 or more and significant growth on 5 μg./ml. or more are taken to mean a high degree of resistance ($++$).

The courses of treatment recorded had been prescribed at a variety of chest clinics, hospitals, and sanatoria, including Hammersmith. The exact dosages and duration of administration of all chemotherapeutic agents given and the serial drug sensitivities were exactly tabulated in their time relationships. This tabulated information was transferred to time charts, enabling the emergence of drug-resistant organisms to be readily seen in relation to previous drug schedules. To illustrate this method four examples are given (Figs. 1–4).

Any factors bearing on the probable degree of co-operation over drug-taking shown by the patients were all recorded; in particular, admissions of failure, their known co-operation in other respects, and the reports of urine-testing for P.A.S. In this way deductions drawn from therapy and resistance records were often reinforced.

Finally, the extent of initial disease, progress, and present clinical status of the patient were all recorded. While no definite conclusions can be drawn from this latter information in a selected group some useful pointers to the significance of drug-resistance were hoped for.

Results

Assessment of the information showed that one main cause usually produced the first resistance to one drug (initial resistance). Because the drug to which the first resistance had developed was often persisted with but

TABLE I.—*Resistances Tabulated According to Type and Drug to Which They Developed*

	Drug to which Resistance Developed			Total
	Streptomycin	Isoniazid	P.A.S.	
Initial resistance ..	18	26	3	47
Subsequent ,, ..	3	3	6	12
Total	21	29	9	59

TABLE II.—*Initial Resistances Tabulated According to Cause and Drug to Which They Developed*

Causes of Resistance	Drugs to which Resistance Developed			Total
	Streptomycin	Isoniazid	P.A.S.	
Faulty prescriptions:				
One drug alone ..	—	6	—	6
Intermittent streptomycin	—	3	—	3
B-P.A.S.	—	2	—	2
Dipasic	—	1	—	1
Thiosemicarbazone ..	—	—	1	1
Oxytetracycline ..	1	—	—	1
Total	1	12	1	14
Failure to take adequate P.A.S. (including 6 prescriptions of combined cachets)	17	14	2	33
Total	18	26	3	47

gave no preventive cover, resistance to other drugs followed (subsequent resistance). A total of 59 examples of drug-resistance developed in 32 patients: 29 under treatment at home, 22 in sanatorium, and 8 in hospital. Of these, 47 were initial resistances and 12 subsequent (Table I). No example of resistance remained unexplained by the method adopted.

The main causes of initial resistance (Table II) were twofold. Firstly, it was deduced that patients failed to take adequate amounts of the prescribed oral P.A.S. in 33 cases (70%). In 27 (58%) the main cause of resistance appeared to be failure to take P.A.S. when prescribed in proper doses *but separate from a second drug* (Figs. 1 and 2). In 6 (13%) cases resistance developed in spite of the prescriptions of P.A.S. plus isoniazid, in correct dosage in *single cachets containing both drugs* (Fig. 3): in one of these the patient admitted to irregular low consumption and in two others the urine tests for P.A.S. were sometimes negative.

Secondly, six varieties of faulty prescription occurred in 14 cases (30%), the commonest being isoniazid given alone. It is suggested that in two cases the explanation lies in the inherent deficiency of calcium benzamidosalicylate (B-P.A.S.). This is likely because these patients, who remain fully sensitive for long periods of treatment with P.A.S. plus one other drug, thus revealing that they took P.A.S. well, yielded resistant organisms

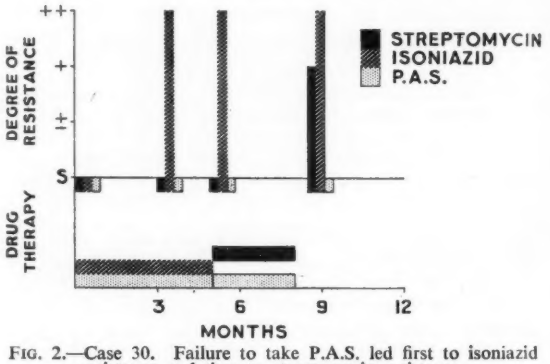

FIG. 2.—Case 30. Failure to take P.A.S. led first to isoniazid resistance and then to streptomycin resistance.

for the first time after changing to B-P.A.S. This is well seen in Fig. 4. The use of a thiosemicarbazone and that of oxytetracycline were both responsible for the development of resistance to an accompanying drug on one occasion each. Both streptomycin used intermittently and the proprietary preparation "dipasic" can also be incriminated.

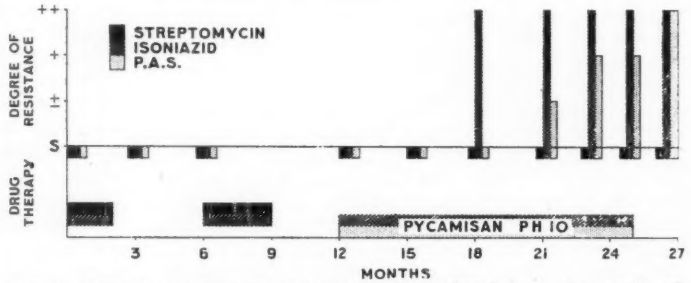

FIG. 3.—Case 13. No resistance to streptomycin developed during five months of treatment with this drug and isoniazid, indicating that the isoniazid was taken. Subsequently, while taking inadequate amounts of "pycamisan," first isoniazid and then P.A.S. resistance followed.

The patients were classified according to extent of disease: 5 slight, 14 moderate, and 13 advanced—N.T.A. (1950) Classification Types 1, 2, and 3. Large cavities were present in six moderate and five advanced cases. With such small numbers, and the original population at risk unknown, it has been impossible to draw any definite conclusions relating this to the emergence of drug-resistant bacterial strains. Suffice it to say that the reasons for the resistance were equally readily found in all three groups and there was no evidence that it developed more quickly in the more advanced cases.

Particularly instructive is an analysis of the present position of the 32 patients. Only eight have quiescent disease and four of these needed major surgery to achieve this end. Of the remaining 24, 9 still have active disease and 15 (47%) have died of their disease. To illustrate the significance of these figures 32 controls

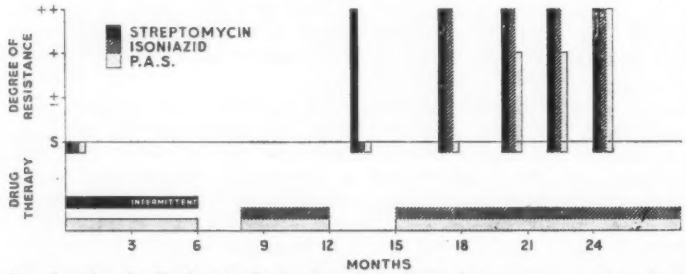

FIG. 1.—Case 3. During the first and second courses of chemotherapy this patient took (by admission) inadequate amounts of P.A.S., leading first to streptomycin resistance and then to isoniazid resistance. Finally, P.A.S. resistance developed after prolonged consumption of inadequate P.A.S. taken with isoniazid to which resistance had already appeared.

were obtained by means of a chronological survey of the clinic notification records. The first patient found matching for date of notification, age, sex, and extent of disease was accepted in each case provided chemotherapy had been given. Only two of these patients have died, and in neither case was death due to tuberculosis (one coronary thrombosis, one cerebral haemorrhage). The remaining 30 controls are alive and well. There is little doubt that the major causative factor for this striking prognostic contrast is the loss of effective chemotherapy following the appearance of resistant organisms.

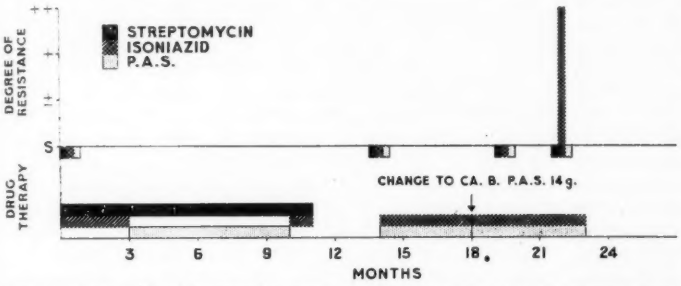

FIG. 4.—Case 5. In this case after seven months' treatment with streptomycin and P.A.S. and four months with isoniazid and P.A.S. the organism remained fully sensitive to all three drugs. This suggests that P.A.S. was taken in effective doses. Resistance to isoniazid appeared only after substituting Ca B-P.A.S. (14 g.) for sodium P.A.S. (10 g.).

Discussion

Apart from prescribing one drug alone, the established cause of the development of resistance to one drug is that the other drug in dual therapy, or the other two in triple therapy, shall be taken in insufficient amount or ineffective form. Confusion may arise, however, over the world-wide divergence of opinion on the degree of bacterial resistance that is clinically significant (International Union against Tuberculosis, 1957). But the use of an insufficiently sensitive drug-resistance test, or the acceptance of too high a threshold for drug resistance, can lead to subsequent resistance to another drug used with that so tested and thus assumed effective. In this study, therefore, as described, bacterial growth on relatively low concentrations of drug in the test media have been accepted as indicating clinically significant resistance. The justification for this is further discussed by Crofton (International Union against Tuberculosis, 1957) and Mitchison and Selkon (1957).

In the light of these facts the results of this investigation suggest that, regardless of whether treatment takes place in the patients' homes or in an institution, or of the extent of the disease initially, the chief cause of the development of resistance lies in the failure to take adequate P.A.S. when administered separately. There was no evidence that patients failed to take separate tablets of isoniazid, and the very fact that six cases of isoniazid resistance developed when this drug was prescribed alone supports this. On the other hand, of the 59 resistances, only 9 developed to P.A.S. (Table I) though that drug was prescribed more often than any other in this series (P.A.S. 156 times; isoniazid 124 times; streptomycin 114 times): resistance cannot develop to a drug that is not taken. A further point supporting the contention that P.A.S. is regularly rejected is related to the faulty prescription of *intermittent* streptomycin plus *daily* P.A.S. or isoniazid. If both drugs are taken in these circumstances P.A.S. or isoniazid resistance, respectively, would be expected. In fact, in this series, nine patients received intermittent streptomycin plus daily P.A.S. and all yielded organisms *resistant to streptomycin but not to P.A.S.*

On the other hand, three prescriptions of intermittent streptomycin plus daily isoniazid led to the expected isoniazid resistance only. Direct evidence, by admission or from urine tests, was obtained that 6 (19%) of the 32 patients had failed to take P.A.S., while 9 others (28%) proved so uncooperative in other ways that co-operation in this respect was unlikely. Because the management of many of these cases antedated the common use of urine tests these figures almost certainly represent an understatement of the true position. It thus seems that there is more to the P.A.S. problem than the well-known occasional forgetfulness to consume a prescribed drug: to produce the results here presented there must be either a regular conscious omission of P.A.S. or doubt thrown upon the capacity of P.A.S. to prevent bacterial resistance to a second drug.

There is nothing new in the conclusion that patients often fail to take P.A.S. (Simpson, 1956; Dixon *et al.*, 1957; Wynn-Williams and Arris, 1958; Fox, 1958; Rigby, 1958), and this is considered to be the most likely explanation for our findings. The results draw attention to the very serious outcome of this habit, so understandable when the drug is distasteful and no particular symptom is being relieved. Only in hospital can the patient be observed regularly when taking his medicine, so that P.A.S. is a very unsatisfactory drug for out-patient use. Even in hospital, however, the utmost vigilance is necessary, as the results show. It is now the practice in our wards at Hammersmith to watch every patient take every dose.

It is our experience that the true magnitude of this problem is still not widely recognized: even in the new edition of *Recent Advances in Respiratory Tuberculosis* (Heaf and Rusby, 1959) the failure to take P.A.S. when prescribed with isoniazid is only mentioned as a temptation, the disadvantage of which can be overcome by prescribing P.A.S. plus isoniazid in the same cachet. This investigation shows, however, that even cachets containing a combination of these drugs in accepted proportions cannot be relied upon to prevent resistance unless a fully effective dose is taken. This is most unfortunate in view of the widespread use of this type of combination under the misapprehension that the patient will either get effective treatment or, if he casts away the cachets, none (and so no resistance); regrettably, patients may take less than the prescribed dose, but reasonably regularly.

The findings also cast doubt upon the effectiveness of the usual dose of B-P.A.S. in preventing the emergence of resistant strains. Furthermore, we are not aware of any convincing evidence that B-P.A.S. is as effective as P.A.S. therapeutically. The *in vitro* experiments of Schönholzer *et al.* (1955) suggest that undissociated B-P.A.S. is a hundred times less effective than P.A.S. The serum levels of P.A.S. after taking B-P.A.S. are much lower than those after taking P.A.S., and the biological activity of the serum is only equivalent to the P.A.S. content (J. McD. Simpson, 1958, and Sheila Stewart, 1958, personal communications). Lewis (1958)

has calculated that to achieve an absorption of P.A.S. equal to that after 20 g. of sodium P.A.S. no less than 48 g. of B-P.A.S. daily would have to be prescribed.

Gibson and Nagley (1955) studied the use of B-P.A.S., but this was not a controlled trial. Many patients received streptomycin three times weekly for only two months (25 g.) so that the chance of the emergence of streptomycin resistance would not be high. From the information presented in their Table 2, relating to 27 patients remaining positive, one hesitates to draw any valid conclusions because so many had received previous chemotherapy and the majority no initial sensitivity tests. Only seven previously untreated patients received chemotherapy for more than three months and one of these for six. In spite of this inadequate period two examples of resistance to the other drug occurred in these seven cases. If therapy had continued further resistances might well have occurred: suboptimum doses of P.A.S. reduce and delay the emergence of resistance but will not prevent it. The paper of Phillips *et al.* (1957), sometimes quoted in support of the ability of B-P.A.S. to prevent drug resistance, gives no precise details of sputum states, drug combinations, or serial resistances. Lewis (1958) also presents evidence suggesting that B-P.A.S. is not effective in preventing the emergence of resistance to other drugs. In the absence of any dependable clinical trial giving clear evidence to the contrary, it is concluded that B-P.A.S. should never be used.

Failure to prescribe effective drug combinations or dosage schedules for newly diagnosed patients was a less frequent but equally important cause of resistance. The faulty schedules which apparently favoured emergence of resistant strains were seen to be varied in this series (Table II). Such prescriptions should now be rare and certainly ought not to be used in the future. Furthermore, to ensure safe treatment for the 5% of newly diagnosed patients who harbour resistant organisms to one of the three standard drugs, it should be an invariable practice to prescribe all three drugs daily to all new patients until drug sensitivities are known. It is implicit in this statement that strenuous efforts must be made to obtain organisms for culture before treatment is started. A little-realized point should be made here: while it is obviously somewhat safer (within the limitations already stated) to prescribe P.A.S. plus isoniazid together in single cachets on those occasions when it is the only possible dual combination, when prescribing the *three* drugs they should be given as *separate* entities. If the P.A.S. is not taken, then the isoniazid is likely to remain coupled with the streptomycin.

With patients previously treated the problem can become acute: it may even be safest to await firm reports on present drug sensitivities before starting treatment, because in certain instances it will be safer to delay treatment than to risk the loss of yet another drug. Thus exceptionally strenuous efforts, using if necessary multiple laryngeal swabs and gastric and bronchial lavages, must be made to obtain a positive culture. The importance of taking a most careful and detailed history of previous drug treatment in such cases cannot be overemphasized: the exact drugs, their dosages, sequence, and duration of prescription, are vital. From such information it is usually possible to hazard correct guesses at the probable drug-resistance pattern of the organism. In particular it is suggested that whenever previous courses of treatment have involved the use of P.A.S., notably in separate form but also in cachets combined with isoniazid, then considerable suspicion should be entertained that a second drug used simultaneously may no longer be effective. Failure to realize this may well lead to multiple resistances and the loss of further drugs. The tragic possibilities are illustrated by the death rate in this series compared with that in the controls. To assist in the full appraisal of such cases a plea is made that hospitals, sanatoria, and clinics dealing with tuberculosis should make available as a first priority, on discharge or transfer, *complete* details of drug courses and sensitivities.

The supreme importance of choosing a drug combination likely to be suitable for a particular patient is thus obvious, but occasionally when faced with a difficult situation there is the temptation to use unproved remedies with apparently quite attractive properties. This can lead to tragic results, particularly if accepted on a nation-wide scale, as, for example, in the case of B-P.A.S. and dipasic. These drugs should never be used—B-P.A.S. since its effectiveness is unproved, dipasic because its therapeutic and antibacterial effects are similar to those of isoniazid, and, when given alone as often recommended, isoniazid resistance develops (Walker *et al.*, 1957; Allan *et al.*, 1957; Williams and Prokopowicz, 1958).

The presence of organisms resistant to even one drug is a clear indication for treatment in hospital until the sputum is negative; the need in such a case to choose a suitable combination of drugs with great care is obvious. When resistance is multiple the judicious use of the more dangerous "second line" drugs, cycloserine, viomycin, pyrazinamide, and 1314, certainly calls for full hospital resources.

The maintenance of drug therapy for at least 18 months is essential to ensure a good response and freedom from relapse (Stewart *et al.*, 1956; Véran *et al.*, 1957; Ross *et al.*, 1958); commonly more is desirable, and anything less should be exceptional. This raises the problem of enforcing correct domiciliary treatment regimes after discharge from hospital. Obviously oral P.A.S. often proves unsatisfactory, and it is recommended that all patients with suitably sensitive organisms should receive daily streptomycin and isoniazid as a standard treatment, with the latter given under supervision at the time of the injection (Stradling, 1957; Dixon *et al.*, 1957). Not only is this combination the best currently available (Medical Research Council, 1955), but it seems to be the only way at present to *ensure* adequate, regular dual-drug therapy. Effort put into making the necessary administrative arrangements (Stradling and Poole, 1958) will be amply repaid.

In circumstances where oral P.A.S. plus isoniazid is the only possible combination because of toxic reactions or an adverse resistance pattern, it is advised that frequent, irregular urine-testing for P.A.S. be resorted to. Every effort should be made to keep the true reason for the tests from the patient, and the test itself should detect only adequate doses of P.A.S. A suitable ferric chloride test is described by Dixon *et al.* (1957). If it is found that the patient is unreliable in any way a decision must be made either to stop treatment or to admit him to hospital: the risk of drug-resistant organisms emerging if out-patient therapy is continued, even if P.A.S. plus isoniazid is given in combined cachet form, is so great that if admission is declined it is safer

to abandon treatment and risk a relapse. At least the organisms present under such circumstances will be fully sensitive and the patient responsive to re-treatment.

Conclusion

The apparent simplicity with which tuberculosis can now be treated is leading many physicians and practitioners to attempt the management of this disease, so long beyond their purview. It is thus opportune and salutary, particularly at this time, when moves are being made to return tuberculosis to the field of general medicine (Joint Tuberculosis Council, 1958), to point out the ease with which fundamental and dangerous errors can be made. All too often the tragic presence of multiple drug-resistant tubercle bacilli is iatrogenic and could have been avoided by the application of basic knowledge. At least two of the three proved drugs should always be used together in long-term treatment and in adequate daily dosage: 1 g. of streptomycin, 200 mg. of isoniazid, and at least 10 g. of P.A.S., though nearer 20 g. of P.A.S. is advisable when given with streptomycin only.

The fact that much of the fault can be ascribed to the patients' failure to consume drugs cannot absolve the medical attendant from responsibility to his patient and—with an infectious disease—to the community. Knowing the position, he should seek means of applying, for an effective period, the forms of therapy which are, on the one hand, least open to criticism by the profession and, on the other, to abuse by the patient.

Summary

An analysis of 32 fully documented case histories yielded 59 examples of drug resistance in *Mycobacterium tuberculosis*.

In 33 (70%) of 47 initially resistant examples the prescription of P.A.S. failed to prevent resistance to the other drug given. By far the most likely explanation of this is that P.A.S. was not consumed in adequate regular amounts. Evidence is also presented that P.A.S. plus isoniazid given together in single cachet form may also not be effective, perhaps for the same reason.

No evidence was found that isoniazid is similarly rejected by patients.

In 14 examples (30%) faulty prescription of drugs was responsible for the resistance. This included the use of one drug alone, prescribing one daily and the other intermittently, the use of such unproved substances as B-P.A.S., dipasic, or a thiosemicarbazone, and also oxytetracycline given with streptomycin.

The importance is stressed (*a*) of using sensitive drug-resistance tests and accepting a low threshold of resistance, (*b*) of scrutinizing a patient's previous therapeutic history and obtaining sensitivities where possible before prescribing further anti-tuberculosis drugs in an effort to avoid resistances, (*c*) of avoiding the prescription of P.A.S. when its administration cannot be fully supervised, (*d*) of never using drugs that have not shown themselves satisfactory in rigidly controlled clinical and bacteriological field trials (B-P.A.S.; dipasic; thiosemicarbazones and their combinations such as "tebafan" and hinconstarch).

It is concluded that, until a more satisfactory oral agent can be found to accompany isoniazid, long-term daily streptomycin given with daily isoniazid is not only the most effective combination therapeutically but the only way of ensuring adequate treatment in spite of the patient's shortcomings.

The ease with which major therapeutic errors can be made with tragic consequences is fully stressed. This point is illustrated by the fact that 15 of the 32 patients in whom drug resistance occurred have since died of their disease: this is in stark contrast to the now usual results of correct long-term chemotherapy.

Our thanks are due to the staff of the Department of Bacteriology, Postgraduate Medical School of London, not only for the unsurpassed routine service provided but for constant advice and encouragement during our management of these difficult cases. Both Professor John Crofton, of Edinburgh, and Dr. D. A. Mitchison, of the Postgraduate Medical School, read the manuscript and offered much helpful constructive criticism.

ADDENDUM.—Since submitting this article for publication our conclusions that (*a*) B-P.A.S. should not be employed, and (*b*) even cachets containing isoniazid and sodium P.A.S. in accepted proportions cannot be relied upon to prevent drug resistance, have been strengthened respectively by Citron and Kuper (1959) and Simpson (1959). A further simple urine test for P.A.S., using "phenistix" (Ames Co., Inc.), has also been investigated by Luntz (1959): we can fully confirm its efficacy and greater simplicity.

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A list of the "Persons Employed in Druggists Shops in Edinburgh on the Sabbath Day" is given in a document, dated 1839, from the pharmacy of H. C. Baildon and Son, Edinburgh, which, with others, has been presented to the Scottish History of Pharmacy Committee. The number employed was 273, to serve a population of about 120,000. (Pharmaceutical Society.)

SUXAMETHONIUM APNOEA IN AN INFANT

EXPRESSION OF FAMILIAL PSEUDOCHOLINESTERASE DEFICIENCY IN THREE GENERATIONS

BY

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The cause of apnoea in association with anaesthesia is often beset with difficulty in interpretation, for so many variable factors may be present. The effects of pre-existing disease may well modify the response of a patient to respiratory depressant drugs, while abdominal surgery is known to cause impairment of respiratory function (Anscombe, 1957). Not infrequently, the label of "scoline apnoea" is applied to the patient who is not breathing at the end of an operation, despite a normal level of plasma pseudocholinesterase. Such an apnoea may be evoked by respiratory depressant drugs in the presence of some pre-operative disability such as emphysema or kyphoscoliosis.

Bourne, Collier, and Somers (1952) and Evans, Gray, Lehmann, and Silk (1952, 1953) drew attention to the prolonged apnoea in man after suxamethonium in the presence of a low pseudocholinesterase. Whereas it had been accepted that plasma cholinesterase could be low owing to acquired deficiency of liver function, Lehmann and Ryan (1956a) observed a familial incidence of low pseudocholinesterase level in the absence of disease. The following report of prolonged apnoea in an infant after suxamethonium shows that this can occur in early infancy, and also contributes new information on the nature of the inheritance of low pseudocholinesterase level.

Case Report

A girl aged 15 months was admitted to hospital for the excision of a small symptomless lumbar meningocele. She was otherwise in good health. Her weight was 13 kg. and haemoglobin 12.3 g./100 ml. Atropine 0.6 mg. intramuscularly was given one hour pre-operatively.

Induction was carried out with cyclopropane and oxygen until the child was asleep, when 20 mg. of suxamethonium chloride was given intravenously and the cyclopropane discontinued. After being inflated with oxygen the child was intubated with a No. 1 flexometallic tube, which was connected to a T-piece and double-ended bag (500 ml. capacity). Artificial respiration with nitrous oxide and oxygen (4 litres/2 litres) was started at the rate of 30–40 a minute. The operation was performed with the child in the prone position, and when it was completed, 45 minutes later, spontaneous respiration was still absent. Discontinuance of the nitrous oxide, movement of the endotracheal tube, painful stimuli, and a few breaths of CO_2 elicited no respiratory response. Fifteen minutes later—that is, 70 minutes after induction—shallow jerky diaphragmatic movements were seen, but respiration had to be augmented for the next two hours until spontaneous respiration was considered to be adequate. Though the child was ventilated with only oxygen from the end of the operation, she did not appear to be awake, though bronchial secretions were profuse and were frequently aspirated. Her temperature was not recorded. Extubation was performed without difficulty, and subsequent recovery was uneventful.

Blood was withdrawn during the period of apnoea for serum pseudocholinesterase estimation. The level of pseudocholinesterase was measured in the serum as described by McArdle (1940). This technique measures the CO_2 liberated from a bicarbonate buffer by the products of ester-hydrolysis. The activity of the enzyme is expressed in units, one unit being equivalent to 1 μl. of CO_2 formed per minute by 1 ml. of serum at 37° C. It was found to be 24 units, which was well below normal. As there was no explanation for the low pseudocholinesterase level, such as liver disease or anaemia, the family of the child was investigated for evidence of familial low pseudocholinesterase level. The findings are recorded in the Diagram.

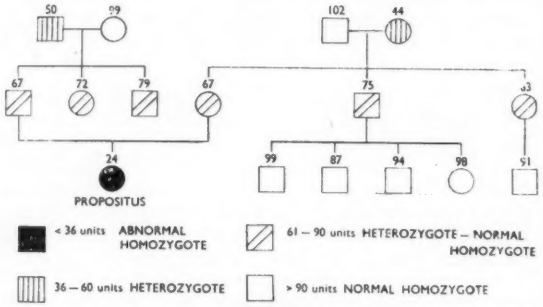

Diagram showing the family tree and the individual pseudocholinesterase levels in units. It is suggested that in the range 61–90 units heterozygotes as well as normal homozygotes can be found.

Discussion

The absence of central respiratory depressant drugs, apart from a few breaths of cyclopropane for induction, suggested the diagnosis of abnormal response to suxamethonium; the low plasma cholinesterase was subsequently confirmed in the laboratory. It is tempting to speculate on the possibility of a further action of suxamethonium besides that of depolarization at the end-plate, for from animal experiments Harmel, King, and Kao (1958) have demonstrated a central effect. Treatment of the apnoea consisted of ventilation until spontaneous respiration became adequate. Drugs were not considered for fear of clouding the diagnosis and possibly even further delaying the return of respiration.

In order for the child to be homozygous for the gene causing a low pseudocholinesterase level, both parents would have to be heterozygotes. McArdle (1940), in a series of normal individuals, found the range of pseudocholinesterase units to be from 55 to 121. From ten years' experience at St. Bartholomew's Hospital, it is considered that a value below 65 units is not truly normal; though, for the purpose of testing the liver function, a result is not reported as significantly abnormal unless it is below 55 units. The parents (67 units) would fall within the lower level of normal individuals, even by the former assessment. However, both parents themselves have one parent in whom the pseudocholinesterase level is definitely abnormally low. Following Allott and Thompson (1956) (see also Lehmann and Ryan, 1956b) Lehmann, Patston, and Ryan (1958) have suggested that there is a considerable overlap of the enzyme levels of heterozygotes and of

normal homozygotes within the range of 61–90 units. Seventeen people with a pseudo-cholinesterase level below 36 units were selected as the propositi of family studies. All of them had come to attention because of suxamethonium apnoea unassociated with a disease which might cause a low pseudo-cholinesterase level. These results can now be further extended by taking into account the present family and eight others examined since, making a total of 26 (Table I).

TABLE I.—*Relatives of Patients Presenting with Suxamethonium Apnoea Unassociated with Diseases Causing a Low Pseudocholinesterase Level*

People with Plasma Pseudocholinesterase <36 Units	Relatives		Plasma Pseudocholinesterase (Warburg Units)			
	Group	No.	<36	36–60	61–90	>90
26	Parents and children	52	3	22	27	0
17	Siblings	31	11	6	11	3
10	Spouses	10	0	0	5	5

If it is presumed that the propositi are homozygous, their first-degree relations—parents and children—should be heterozygotes. It is clear from Table I that none of 52 first-degree relatives of the 23 propositi had a pseudocholinesterase level above 90 units. Thus it can be considered fairly safe to rule out the heterozygous state for the abnormal gene when a level above 90 units is found. On the other hand, more than half of the 52 first-degree relations assumed to be heterozygotes showed a pseudocholinesterase level within the lower range of normality—from 61 to 90 units. Thus, within this range an overlap occurs between normal homozygotes and heterozygous carriers. The present family tree shows this particularly well. The enzyme levels of both parents of the propositus are found within this "normal" range—61 to 90 units. Yet each of these two, in turn, has one parent with a clearly abnormally low level of 50 and 44 units, respectively. Together they have a child with an enzyme level of 24 units.

There is, obviously, also an overlap at the lower range of the enzyme levels, and values below 36 units seem to include both abnormal homozygotes and heterozygous carriers. Three individuals in the parents-and-children group (Table I) showed values of less than 36 units (26, 28, and 35 units, respectively), and two of these were children of a propositus and a spouse with a pseudocholinesterase level above 90 units. Thus, in at least two of these it seems possible to rule out the homozygous state. Not enough data have yet been accumu'ated, but it may well be that the values below 36 units will have to be subdivided into those below 26 units, designating definite abnormal homozygotes, and those from 26 to 35 units, designating both abnormal homozygotes and heterozygotes. Kalow and Staron (1957) have demonstrated that an abnormal enzyme can be the cause of idiopathic familial low pseudocholinesterase level. Investigations are in progress, in collaboration with Dr. H. Harris and Dr. Mary Whittaker, London Hospital Medical College, to examine the correlation between the findings of the Canadian workers and those of this country. Possibly these studies will throw light on the subdivision of phenotypes proposed in Table II.

TABLE II.—*Abnormal Gene Causing Low Pseudocholinesterase Level*

Pseudocholinesterase	Abnormal Homozygotes	Heterozygotes	Normal Homozygotes
<26 units	+		
26–35 "	+	+	
36–60 "		+	
61–90 "		+	+
>90 "			+

Summary

Suxamethonium apnoea is described in a child aged 15 months. This is believed to be the first such recorded observation in an infant. The family has been studied in detail. There was a deficiency of pseudocholinesterase in one paternal and in one maternal grandparent, yet only low normal values for pseudocholinesterase were found in both parents. The overlap of enzyme levels found for presumed heterozygotes for the abnormal pseudocholinesterase gene and for normal individuals is discussed.

We are grateful to Mr. G. H. Macnab, under whose care the patient was admitted into the Hospital for Sick Children, Great Ormond Street, London, and to Dr. R. W. Cope for their permission to use the case notes of this patient.

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EOSINOPHILIA IN CHILDREN WITH ASTHMA AND BRONCHIECTASIS

BY

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It is well known that asthmatic attacks are often associated with an eosinophilia in the circulating blood and that the bronchial secretions also may contain an excess of eosinophils (Stickney and Heck, 1944 ; Urbach and Gottlieb, 1946). Blood eosinophilia is regarded as typical of allergic reactions in general, and can be produced experimentally by injections of protein material (Biggart, 1932) or histamine (Vaughn, 1953). It is suggested that the eosinophils are concerned in the transport of histamine which is produced in allergic reactions (Code, 1952 ; Vaughn, 1953).

The present paper provides evidence that eosinophilia in asthmatic children is not confined to the times of the asthmatic attacks and in general is unrelated to the degree of ventilatory impairment. In addition, eosinophil counts on a group of children with asthma and a group with bronchiectasis are compared in order to evaluate their usefulness in differentiating these conditions.

Methods

Eosinophil counts were performed on 83 children (40 with bronchiectasis and 43 with asthma). These were

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carried out at routine clinical attendances without regard to the child's condition at the time.

All the asthmatic patients had had typical paroxysms of breathlessness and wheezing within the previous 12 months. Four of them produced small amounts of purulent sputum but were otherwise typical and severe examples of the condition.

All the patients with bronchiectasis had permanent cough with purulent sputum and persistent abnormal segmental shadows on plain radiographs of the chest; the presence of bronchiectasis had been confirmed by bronchography in 35 of them.

The ventilatory capacity in terms of the forced expiratory volume in one second ($F.E.V._1$) had been found to be a satisfactory objective measurement of the severity of asthma in children (Strang, to be published). In order to compare this with the level of blood eosinophilia, a group of 14 children with asthma were seen as out-patients at 14-day intervals for a period of six months (182 examinations), when the $F.E.V._1$ was measured and the eosinophils were counted. Though it was not anticipated in the plan, a number of attacks of clinical influenza occurred in these patients, and these events were recorded. The procedure for measuring the $F.E.V._1$ was the same as described elsewhere (Strang, 1959). Eosinophil counts were done on ear-prick samples by the direct enumeration technique of Randolph (1944).

Comparison of Eosinophil Counts in Children with Asthma and Bronchiectasis

The initial eosinophil count performed on each child was regarded as a random observation, and therefore as a fair basis for comparison between children with asthma and those with bronchiectasis. The results (Fig. 1) show a large and obvious difference in the two groups with only a small overlap. Eosinophilia of over 600/c.mm. was present in 37 out of 43 patients with asthma, and

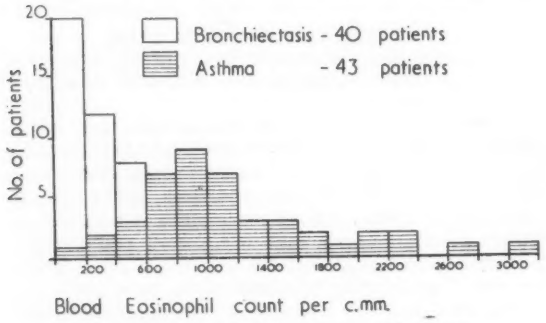

FIG. 1.—Initial eosinophil counts on 83 patients.

in none of 40 with bronchiectasis. A second count in 30 of the asthmatics failed to reveal an eosinophilia in only two.

The initial eosinophil counts on the four asthmatic children who had purulent sputum were 1,085, 2,175, 1,530, and 1,175/c.mm.

Serial Observations of Eosinophil Count and Ventilatory Capacity in 14 Children with Asthma

Serial observations showed that eosinophilia was very persistent in these patients. A typical record of eosinophil counts and F.E.V.s in one child is presented in Fig. 2

Low counts were infrequent, a count below 350/c.mm. occurring on 11 occasions only. On seven of these it was recorded that the child was suffering from or just recovering from an illness regarded as influenza. In fact, the seven recorded infections occurred within a period of 28 days at a time when influenza B infections were known to be very common. Two of the four remaining low counts occurred during the same 28-day period.

A comparison of eosinophil counts and ventilatory measurements is presented in the Table. To allow comparison between children of different size the

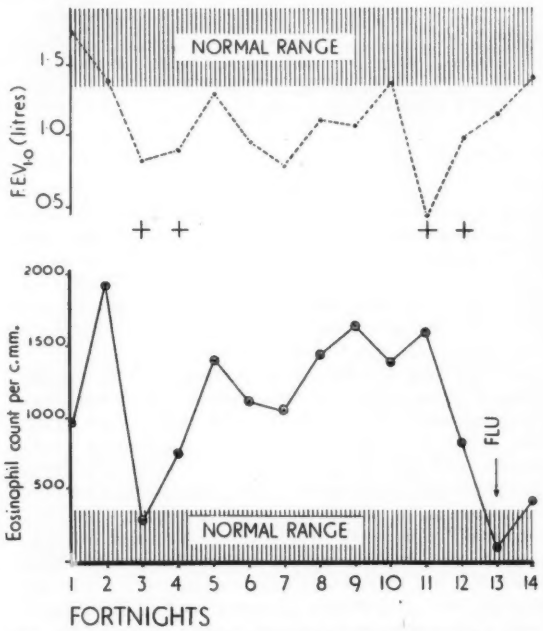

FIG. 2.—Serial observations of F.E.V. and eosinophils in one child (No. 12). + Signs indicate generalized rhonchi on auscultation.

$F.E.V._1$ is expressed as a percentage of normal for height (Strang, 1959). The correlation between the eosinophil count and the $F.E.V._1$ in the pooled results was not significant, nor between the individual mean values of eosinophils and $F.E.V._1$. One child (No. 2) had a significant negative correlation, worsening of his asthma being associated with increasing eosinophil counts.

Eosinophil Count (per c.mm.)+F.E.V.$_1$ (percentage normal) in 14 Asthmatic Children—Means, Standard Errors, and Correlations

No.	Mean Eosinophil Count (S.E.)	Mean $F.E.V._1$ (S.E.)	No. of Observations	Correlation Coefficient	P
1	943 (94)	51 (4·4)	11	+0·230	>0·05
2	770 (92)	56 (2·9)	15	−0·760	<0·05
3	668 (94)	82 (3·5)	13	+0·315	>0·05
4	645 (77)	65 (4·5)	13	+0·154	>0·05
5	804 (56)	67 (1·5)	15	+0·208	>0·05
6	549 (65)	76 (10·8)	13	−0·176	>0·05
7	1,596 (240)	115 (1·9)	12	+0·463	>0·05
8	1,072 (196)	79 (3·1)	11	+0·536	>0·05
9	1,097 (101)	39 (1·7)	12	+0·160	>0·05
10	713 (110)	61 (3·7)	13	+0·151	>0·05
11	893 (107)	36 (4·2)	13	+0·364	>0·05
12	1,072 (144)	66 (5·0)	14	+0·255	>0·05
13	1,191 (103)	40 (2·5)	14	+0·080	>0·05
14	1,235 (193)	58 (2·1)	13	+0·045	>0·05

Correlation coefficient for pooled results = +0·135 (n = 182; P>0·05).
Correlation coefficient between mean values of $F.E.V._1$ and eosinophil count = +0·175 (n = 14; P>0·05).

However, the trend in the other children was in an opposite direction, the association being between increasing eosinophil counts and improvement. Indeed, 12 of the 14 correlation coefficients were of the same (positive) sign, and by the sign test this trend is significant at the 5% level. There was no obvious clinical difference between Case 2 and the other children, but if he were excluded the correlation coefficient for the remainder would be positive and significant ($r = +0.203$; $n = 167$; $P<0.05$).

Discussion

Though the association of asthma and eosinophilia is well known, it is surprising to find that random eosinophil counts in a group of asthmatic children so often show abnormally high levels. That this state of affairs is not commonly recognized is revealed by a question published in the *Journal of the American Medical Association* (1955), which sought an explanation for persistent eosinophilia in a child with asthma. Two experts, in answering the question, regarded the finding as unusual and suggested investigations for parasitic infection.

In this material eosinophilia is very persistent in asthmatic children and in general is unrelated to the severity of the asthma. The trend, if anything, is the opposite of that expected, the higher levels of eosinophilia being associated with the better ventilatory performances.

By chance, marked falls in the eosinophil count were noted in response to apparent possibly influenzal infections. This observation should be extended by further observations on a variety of infections in asthmatics.

In children with bronchiectasis there is no evidence of an associated eosinophilia, and because of this the eosinophil count may help to differentiate the two conditions. This may be unnecessary in clear-cut examples, but, in fact, the clinical syndromes may overlap. Thus children with bronchiectasis have attacks of noisy breathing which have been described as wheezing (Field, 1949), and they can be shown frequently to have a ventilatory impairment associated with bronchial obstruction (Strang, to be published). In addition, the bronchial dilatations long regarded as the characteristic feature of the disease may be quite insignificant and unrelated to the extent of severity of bronchial damage (Whitwell, 1952). On the other hand, asthmatic children sometimes develop a persistent cough and sputum, which in a few of them is purulent. Both conditions probably include examples of early or potential chronic bronchitis, which may be a final common path for some of these children.

In any scientific study of bronchitis in children it would be very important to distinguish asthma from bronchiectasis or other categories. Eosinophilia appears to be a sufficiently constant feature of asthma to serve as a basis for such a differentiation.

Summary

Eosinophilia is common and very persistent in children with asthma. The height of the eosinophil count is unrelated to the severity of the condition as measured by the $F.E.V._1$. The eosinophil count is not raised in bronchiectasis, and it may serve as a means of distinguishing these conditions in borderline cases and in scientific investigations of bronchitis in childhood.

Thanks are due to Professor S. D. M. Court for helpful criticisms, and to Dr. E. G. Knox and Mr. D. Newall for statistical advice.

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DOG-BITES AND LOCAL INFECTION WITH PASTEURELLA SEPTICA

BY

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AND

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Dog-bites are common; we see over a hundred new patients with this injury in our accident service annually. The present investigation was carried out to examine the therapeutic management of dog-bites, and, in particular, bites infected with *Pasteurella septica*. Human *P. septica* infection following these bites is thought to be rare—only five cases have been recorded in this country (Allott *et al.*, 1944; Brunsdon and Mallett, 1953; Emson, 1957); we found 12 additional cases in a review of our records.

Present Investigation

Material.—The records of 69 patients (1952–7) who had suffered dog-bites which had been investigated bacteriologically were reviewed. (No bacteriological examination had been made of the wounds of the other patients who suffered dog-bites during this period.) Of this number, 39 were adults and 30 were children under 13 years of age. Swabs from 59 of these wounds were taken on the first day of attendance at hospital, as they were thought to be contaminated wounds. The remaining 10 were swabbed some days later, when it became apparent that a wound infection had developed. All swabs were cultured both by aerobic and by anaerobic methods.

Site of Injury.—The location of these bites was: face, 19 (17 children); upper limb 32 (8 children); lower limb, 18 (5 children).

Treatment. — Tetanus toxoid or antiserum was administered. No situation arose in which it was considered necessary to give antirabic serum or vaccine. Wounds were cleansed with a detergent and left unsutured in 39 instances in accordance with accepted practice. In 30 patients it was thought advisable to carry out excision and suture after careful wound toilet. Prophylactic penicillin therapy was given in only nine cases, in three of which the bite had been sutured; all these nine patients attended hospital on the day of injury.

Wound Infection. — Frank infection of wounds developed in 20 (29%) cases. Of the 17 children bitten on the face, five developed wound infection. Of the 30

wounds that were sutured, 14 (47%) became infected. Only one of the nine patients who received prophylactic penicillin developed a wound infection.

Bacteriology

The culture reports on the 20 bites which became infected are shown in Table I.

P. septica was cultured from 12 (17%) wounds. Ten of these became infected, accounting for 50% of infected bites. Prophylactic penicillin had been given to the two patients who did not develop a wound infection; one of these wounds had been sutured.

TABLE I.—*Organisms Found in 20 Infected Bites*

	No. of Cases
**P. septica* (in pure culture)	5
**P. septica* + Beta-haemolytic streptococcus, Group C	1
**P. septica* + Paracolon	1
P. septica + Micrococci + *Streptococcus viridans*	1
P. septica + *Str. viridans*	1
P. septica + Neisseria	1
Staph. aureus (penicillin-sensitive)	2
Micrococci	1
Staph. aureus (penicillin-sensitive) + Beta-haemolytic streptococcus, Group A	1
Clostridium welchii + *Staph. aureus* (penicillin-sensitive)	1
Staph. aureus (penicillin-sensitive) + Alpha-haemolytic streptococcus + Beta-haemolytic streptococcus, Group G + *Str. viridans*	1
"Sterile"	4

* Bacteriological examination of these wounds and three of the "sterile" wounds was carried out because infection developed.

In six instances one or more micro-organisms were cultured in addition to *P. septica*. Five of these wounds, all sutured, developed frank infection. The one bite that did not become infected was not sutured but received systemic prophylactic penicillin. One bite that was sutured under penicillin cover became infected; bacteriological examination of this wound on the ninth day revealed a penicillin-sensitive *Staph. aureus*, and on the 24th day *P. septica*. This was the only instance in which the two organisms were associated.

From the 49 wounds that did not become infected the following organisms were cultured in addition to those found in the infected wounds: *Pseudomonas pyocyanea*, *Achromobacter Bacillus anitratus*, pneumococci, diphtheroids, *Proteus vulgaris*, aerobic spore-bearing organisms. Ten of these 49 wounds were sterile on culture. Six of these 49 patients received prophylactic penicillin, but there was no common bacteriological pattern in the wounds so protected.

Other Data

Average Duration of Hospital Attendance.—Patients who for various reasons completed part or most of their treatment under the care of their family doctor are not included except as shown.

Not infected	9.5 days
All types of wound infection	22.5 ,,
**P. septica* wound infection	21.7 ,,

*Three other patients were referred to the care of their own practitioners to carry on dressings after 23, 21, and 15 days respectively.

Seasonal Incidence.—This is shown in Table II; we have included the five previously reported cases for comparison. G. H. Tee (personal communication) isolated *P. septica* from 12 dog-bites during the period April to September, and 16 dog-bites from October to March, during the past three years. The above distribution is of interest in the light of the observations

TABLE II.—*Seasonal Incidence*

Month:	J.	F.	M.	A.	M.	J.	J.	A.	S.	O.	N.	D.
Allott *et al.* (1944)	1									1		1
Brunsdon and Mallett (1953)									1		1	
Emson (1957) Oxford	1			1	1		1	1	3	3		1
	2			1	1		1	1	4	4	1	2

by Smith (1955), who isolated *P. septica* from the nose, tonsils, or both nose and tonsils of 55% of healthy dogs; he also noted that the higher incidence of *P. septica* in the nose during the winter months may also be connected with the epidemiology of canine distemper, a disease which is most prevalent during the colder half of the year, particularly in the late autumn and early spring. The seasonal variations in the nasal carrier rate of *P. septica* in dogs resemble those recorded by Straker *et al.* (1939) for pneumococci in the human subject.

Discussion

P. septica (*P. multocida*) has been reported as an upper-respiratory-tract commensal in dogs, cats, rabbits, pigs, and other animals. Human infection with this organism following cat-bites has been noted fairly often. Apparently only five examples of human infection with *P. septica* following dog-bites have been previously recorded in this country (see Table II).

Wounds infected by this organism are generally characterized by a prolonged period of treatment and occasionally complicated by infection of underlying bone. Allott *et al.* (1944) gave an account of six patients whose wounds were infected with *P. septica*—three following dog-bites and three following cat-bites; these patients attended hospital for treatment for an average period of nearly 50 days; "subacute osteomyelitis was a complication in three of the cases." Allin (1942) and Cooper and Moore (1945) also recorded bone infection following *P. septica* infection of a soft-tissue cat-bite. None of our patients with *P. septica* infection had bone involvement.

Emson (1957) summarized the literature on human infections with *P. septica* and covered in detail the bacteriology, biochemistry, serology, and classification of this organism.

Schipper (1947) studied 14 strains of *P. septica* (*P. multocida*) and additional strains from other laboratories; all strains were sensitive *in vitro* to less than 0.2 unit of penicillin per ml. of media. This extreme sensitivity to penicillin is rather unusual for a Gram-negative rod, and he suggested that this might be used as an additional method for differentiating this organism from other Gram-negative micro-organisms. Olsen and Needham (1952) reported 37 cases of *P. septica* isolated from patients with suppurative diseases of the respiratory tract and noted that this organism "is rapidly eradicated by penicillin therapy."

Summary and Conclusions

Of 69 cases of dog-bite investigated bacteriologically 20 (29%) developed frank wound infection.

Fourteen (47%) of the 30 wounds that were sutured became infected.

Only one of the group of nine patients who had prophylactic penicillin therapy developed a wound infection.

P. septica, an organism sensitive to penicillin in normal therapeutic doses, was cultured from 12 (17%) wounds. Ten of these became infected, accounting for 50% of infected lesions. Only five other local infections with *P. septica* following dog-bites have been reported in this country. Routine bacteriological examination of these bites might show that this type of infection is fairly common.

Infected bites are characterized by prolonged treatment and unsightly scars. Since many children are bitten by dogs and the bite is commonly received on the face, it is obviously desirable to ensure healing with minimal scarring.

There is evidence here to suggest that prophylactic penicillin therapy should be given to all patients with serious dog-bites and particularly to those whose bites have been sutured.

We thank Mr. J. C. Scott, director of the Accident Service, for his interest and help; Dr. R. L. Vollum, bacteriologist to the United Oxford Hospitals, for his advice and encouragement; and Dr. G. H. Tee, director of the Public Health Laboratory, Dorchester, for allowing us to use some previously unpublished data.

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HAEMATEMESIS AND/OR MELAENA FROM PEPTIC ULCER

SHORTER CONSERVATIVE MANAGEMENT

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The ideal duration of hospital treatment after haematemesis or melaena from peptic ulcer once massive bleeding has stopped is undecided. Most authorities have disregarded what the necessary length of bed rest should be, but it is often suggested that four to six weeks' bed rest is required, as for active chronic peptic ulcer.

The records from the Central Middlesex Hospital for 1956 show that after haematemesis or melaena 63 males and 40 females were treated conservatively as in-patients for an average of 21 days (males 22; females 19.5). The same average stay of 21 days was found for 34 patients treated at the Middlesex Hospital between August, 1957, and June, 1958. In the Portsmouth Group of Hospitals, however, they are kept in longer: an average of 34 days for 44 patients admitted between January and November, 1958. Many factors may be involved in this difference, but among them must be a difference of policy respecting bed rest. This is borne out by the variation found if the figures are analysed for each physician separately.

In view of the obvious social and economic benefits from early discharge from hospital it is important to establish whether there is any medical contraindication to early mobilization. We have therefore compared two groups of patients, one mobilized immediately major bleeding ceased and the other kept in bed, and therefore also in hospital, for one week longer.

Material and Methods

85 male patients were admitted to the department of gastro-enterology, Central Middlesex Hospital, between October 15, 1957, and September 1, 1958, with major gastro-duodenal bleeding assumed to be due to peptic ulcer. For administrative convenience, and because a review of earlier records showed no difference with regard to sex in customary management, only males were studied. Nineteen patients were excluded for the following reasons: emergency surgery for haemorrhage (16), death from cerebral hypoxia shortly after admission (1), mediastinal emphysema after oesophagoscopy (1), and complicating pneumonia and cerebral thrombosis (1). There thus remained 66 patients.

Patients were allocated to one of two groups, "Up" and "Bed," by drawing lots as soon as bleeding had ceased ("D day"). This was judged particularly by the cessation of haematemesis or loose melaena stools, and by a stable pulse and blood-pressure. The haemoglobin level was above 7.4 g./100 ml. (50%) at this time, and blood transfusions were given where necessary to ensure this.

The up group was then mobilized as follows:

Day D+1—Sitting out for three hours and one visit to toilet.
Day D+2—Walking for two hours and visiting toilet at will.
Day D+3 and thereafter—Ambulant all day.

The bed group was kept at rest for a further week and then mobilized in the same way.

All patients received a standard convalescent gastric diet with antacids as desired. Blood transfusion was used to treat shock and to keep the haemoglobin at a satisfactory level (Avery Jones, 1952). Oral iron (ferrous gluconate tablets, *B.P.*, 300 mg. t.d.s., or ferrous sulphate tablets, *B.P.*, 200 mg. t.d.s.) was given to all anaemic patients from D day onwards. Barium-meal examination was performed in all except two patients as soon as practicable after mobilization. Gastroscopy was carried out in 38 patients. When no lesion was seen by either radiology or gastroscopy, and bleeding appeared on clinical grounds to be due to peptic ulceration, an acute ulcer was presumed responsible. Haemoglobin levels were estimated daily before D day and at least twice a week thereafter, using a standard procedure. On leaving hospital, patients were fully ambulant, free from anaemia, and without significant dyspepsia. They were seen in the out-patient department at three weeks and six weeks after D day, when symptoms were reassessed and the

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haemoglobin was estimated. Ten patients failed to attend the follow-up at six weeks. Of these, eight were contacted by letter, but two (one from each group) had left the district and were untraceable.

Results

Each group contained 33 patients and was comparable to the other in age distribution (Table I), diagnosis (Table II), and the severity of bleeding (Table III). This last was judged by the greatest degree of anaemia (see Chart), the volume of blood transfused, and the interval between admission and D day. Possible precipitating factors of haemorrhage were salicylate consumption (28 patients), alcoholic excess (6), and infections (3, all of whom also took salicylates). These factors were also equally common in the two groups.

The progress of the two groups was compared for symptoms and complications, the length of hospital stay and of time lost from work, and the rise of haemoglobin (Tables IV and V, and Chart). On average the up patients stayed in hospital for 11 days and were off work for 27 days, while the bed patients were in for 18 days and off work for 38 days. The rise of haemoglobin was satisfactory, and comparable in the two groups. However, the incidence of complications, particularly of recurrent haemorrhage and severe dyspepsia, was lower in the up than in the bed patients.

TABLE I.—*Age Distribution*

	20–29	30–39	40–49	50–59	60–69	70–79	80+	Average
Up group ..	3	3	7	13	2	4	1	54 years
Bed group	5	3	7	6	7	4	1	51 years

TABLE II.—*Diagnosis*

	Duodenal Ulcer	Gastric Ulcer		Stomal Ulcer	No Lesion Found
		Chronic	Acute		
Up group ..	16	6	1*	2*	9
Bed group ..	18	3	1	—	11

* 1 patient had a stomal ulcer and an acute gastric ulcer.

TABLE III.—*Severity of Illness*

Transfusion before D day

	Patients transfused	Average No. (and range) of pints per patient transfused
Up group	17 (51·5%)	4·9 (2–16)
Bed group	16 (48·5%)	4·8 (2–15)

Interval (days) between admission and D day

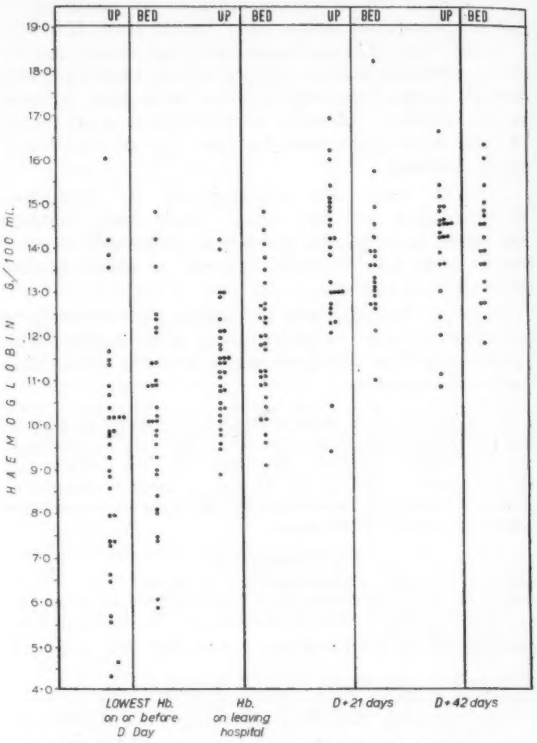
	2	3	4	5	6	7	Average
Up group ..	6	14	7	6	—	—	3·4 days
Bed group ..	8	12	7	2	3	1	3·5 days

TABLE IV.—*Complications After D Day*

Complications	Up group	Bed group
Recurrent bleeding :		
Not requiring transfusion	1	1
Requiring transfusion	3 (2·3 pints/patient)	5 (3·8 pints/patient)
Requiring surgery ..	—	2 (after leaving hospital but within 6 weeks of D day)
Severe dyspepsia :		
Not requiring surgery	—	3
Surgical treatment ..	1	1
Perforation	—	1 (died)
Leg-vein thromboses ..	1	—
Total	6	13

TABLE V

	Average Stay	Range	Exclusions
Length of Stay in Hospital (in Days)			
Up (31 patients)	10·9	7–18	Elective surgery, 2
Bed (30 patients)	17·6	14–27	Elective surgery, 1. Died, 2
Length of Time off Work (in Days)			
Up (24 patients)	26·9	14–56	Retired, 6. Elective surgery, 3
Bed (21 patients)	37·7	18–71	Retired, 6. Elective surgery, 3, Died, 2. Untraced, 1.



Haemoglobin levels in both groups at different times.

A barium-meal examination was performed on average on the fifth day after D day in the up patients (range 2–10), and on the 11th day after D day in the bed patients (range 1–22). In addition, three emergency barium-meal examinations were performed during massive bleeding, on patients who subsequently had emergency surgery. In no case was any ill effect seen.

Gastroscopy was carried out in 38 patients, and in only seven was a lesion seen. Of 31 negative examinations, a duodenal ulcer was later seen radiologically in 17, while in 13 patients no radiological lesion was seen. Of these 13, 9 had their gastroscopy within three days of admission.

Discussion

This study has shown that patients mobilized rapidly after haematemesis and/or melaena progressed as well in every respect as those kept in bed a week longer. The complications in the up patients were in fact fewer than in the bed patients, but the significance of this is uncertain because of the small numbers. The up regime is particularly advantageous from the social and economic aspects. The patient's satisfaction from

his early return home and the economic gain from an early return to work must be appreciated, as well as the saving in hospital beds [calculated for this hospital for 1956 as 1,040 bed days (or £3,250)].

Prolonged bed rest is traditionally recommended in the treatment of active chronic ulcer, but it does not seem to be necessary in cases of haemorrhage. One reason may be that bleeding unrelated to progressive chronic ulceration may occur in response to salicylates (Douthwaite, 1938; Muir and Cossar, 1955; Alvarez and Summerskill, 1958), to alcohol, to infection, or to unknown stimuli. The number of patients who had consumed salicylates within the 48 hours prior to bleeding (42%) agrees with the findings of Alvarez and Summerskill (1958) in this hospital in 1957. Another reason is that patients bleeding from severe progressive ulceration often need emergency surgery and so have not been studied here. Such patients may also account for the serious complications after D day which occurred during and in spite of bed rest.

Early discharge from hospital necessitates early radiological examination for diagnostic purposes. It has been held that a barium-meal examination too soon after bleeding might restart haemorrhage, but Zamcheck *et al.* (1952) and Zamcheck (1955) showed that immediate examination is both safe and reliable, and that patients tolerate the standing position for radiology better soon after admission than after bed rest. Certainly, no ill effects occurred in this series with moderately early barium-meal examinations.

Only seven lesions were seen in 38 gastroscopies, probably because the study was limited to male patients, who have a high ratio of duodenal to gastric ulcers (Avery Jones, 1957), while cases of carcinoma of the stomach were excluded. The low proportion of acute lesions visualized was not due to delay in performing the examination, and the presence of blood in the stomach did not often invalidate the procedure.

Summary

The necessary duration of bed rest in hospital after haematemesis and malaena from peptic ulcer has been studied by comparing the progress of two groups of patients, one mobilized quickly and the other slowly.

Patients mobilized as soon as massive haemorrhage had stopped did as well as those kept in bed.

Rapid mobilization involved radiological examination soon after haemorrhage had ceased, and no ill effects occurred as a result of this.

Our thanks are due to Dr. F. Avery Jones, and to the staff of the department of gastro-enterology, Central Middlesex Hospital, for their help. We also thank the Medical Committee of the Middlesex Hospital and the consultant physicians of the Portsmouth Group of Hospitals for permission to study their case notes.

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Medical Memoranda

Cadmium Poisoning

Cadmium is largely obtained in the smelting of impure zinc ores as a by-product and less often as a mineral called greenockite, which is cadmium sulphide. Cadmium can be highly polished and has good anti-corrosion properties (Heyroth, 1949). If slightly overheated, molten cadmium readily ignites. Its vapour is heavier than air and burns with a bright flame producing brown fumes of cadmium oxide. Cadmium as a fume is very toxic (Elkins, 1959). If the metal is heated, as in welding, fumes of cadmium oxide are emitted which are responsible for the toxic effects when inhaled from the working atmosphere. Even small amounts of molten cadmium can produce a toxic concentration of fumes. Cadmium vapour condenses in the air and is inhaled as a smoke of finely divided particles. A dust hazard may develop from grinding, cutting, or handling the dry powder. Probably the most hazardous compound of cadmium is the oxide, which is an acute irritant affecting mainly the eyes, nose, throat, and lungs.

In acute cadmium poisoning the patient develops sore eyes, dryness of the throat, tightness of the chest, breathlessness on slight exertion, and cough. In a few hours he may have nausea, vomiting, shivering, general weakness, and pains in the joints. Pneumonitis may develop. Death may be due to pulmonary oedema or bronchopneumonia. At post-mortem examination cadmium is found particularly in the lungs, kidneys, and liver (Elkins, 1959).

Chronic cadmium poisoning may occur through long-continued exposure to the fume or dust. The patients develop lassitude, chronic cough, and dyspnoea due to emphysema. This may be associated with recurrent epistaxis, anosmia, and irritation of the throat. Cadmium is excreted in the urine, but its presence alone without symptoms does not warrant the diagnosis of cadmium poisoning. In chronic poisoning there is sometimes renal excretion of a protein of low molecular weight which is detectable by the sulphosalicylic acid test (Bonnell *et al.*, 1959).

Cadmium-plated articles should not be used for the preparation of food because of the possible irritant effects on the gastro-intestinal tract, causing an acute gastro-enteritis which is usually rapid in onset (Fairhall, 1949; Sax, 1957). This condition can be treated by administering albumin (Dickinson, 1948).

The maximum allowable concentration of cadmium as recommended by the American Conference of Industrial Hygienists is 100 μg./c.cm. (Sax, 1957). Local extract ventilation is necessary in processes involving a potential hazard from cadmium dust or fume, such as smelting, casting, grinding, or hot-metal spraying.

In the United Kingdom, under the National Insurance (Industrial Injuries) Act, 1946, certain occupational diseases are prescribed for industrial injuries benefit. Poisoning by cadmium is one of the prescribed diseases.

INDUSTRIAL USES

In electronics cadmium-plated steel chassis are used in view of the low electrical potential between the two

metals. In the atomic pile cadmium-coated control rods are used because this metal is a very good absorber of neutrons. The speed of the reaction can be controlled by the depth of penetration of the control rods (Sears, 1953). In view of the intensity of radiation the rods must be operated by remote control. Cadmium-plating has good anti-corrosion properties, and alkaline electric accumulators are manufactured with a cadmium cathode. Smelting and casting of cadmium occur in the manufacturing processes and in separating it from zinc ores. Copper–cadmium alloy is used for electric power cables and overhead wires for trolley buses (Hunter, 1955) because the cadmium improves wear and strength of copper without a significant change in the electrical conductivity.

Cadmium-spraying of the molten metal is used both to coat and to build up metals, such as bearings. The halides of the metal are employed in photography. The salts, notably the sulphide, are used as pigment in paints and for the colouring of glass. Cadmium carbonate, as a silver polish, caused the earliest reported case of cadmium poisoning in 1858. Cadmium oxide has been used in the chemical industry for coating luminescent powders and as a catalyst for the manufacture of highly unsaturated alcohols by hydrogenation of unsaturated fatty acids or their esters. It is also used to sensitize the photochemical reaction for formation of hydrogen peroxide from water (Dickinson, 1948).

CASE HISTORY

A man aged 60 reported to his works medical department, giving the following history. The previous day he had been working in a modern airy shop without any form of forced extract ventilation. He had been cutting scrap metal with a welder's torch for about five hours. This process produced fumes which irritated his eyes, nose, and inside his chest. After several hours his legs began to feel weak, and during the afternoon he had a frontal headache with generalized aches and pains. When he got home he felt cold, so went to bed very early. He sweated profusely and had little sleep. His respirations became rapid, but he had no cough, tightness of the chest, nausea, or diarrhoea. Next morning he was feeling more comfortable, but the frontal headache remained, though it was less severe. He went to work as usual, but was persuaded by other workers to report to the works medical department. He was reluctant to do this, but fortunately was prevailed upon to attend. He reported during the afternoon of the day following the incident. At that time he complained of a slight frontal headache and some abdominal discomfort. The general malaise had gone. The eyes, nose, throat, cardiovascular system, and chest were all normal. A chest *x*-ray film showed no significant change compared with a routine film taken about five months before.

He had a history of duodenal ulcer, and the last time he had had epigastric pains was six weeks prior to the present incident.

About 48 hours after the incident he complained of undue breathlessness on walking, with tightness across the front of the chest. He again had general malaise and felt weak. At this stage no abnormal physical signs were detected in his chest. He had to go to bed for several days.

On the 14th day he was seen again, when he felt much better. He still had some undue breathlessness on walking and tightness across the front of the chest on full inspiration. His eyes, nose, throat, heart, and chest were normal. The chest *x*-ray film remained unchanged. A full blood count revealed no abnormality. The urine was tested with sulphosalicylic acid, but no proteinuria was detected and there was no reduction of Benedict's reagent.

All symptoms had cleared within four and a half weeks.

Treatment.—In the above case only symptomatic treatment was required. An apparently highly successful method of treatment has been reported. This consists in prescribing 0.5 g. of edathamil calcium-disodium (calcium disodium versenate ; E.D.T.A.) as a pill every two hours during the day while the patient is awake, for one week. It is recommended that one week after the end of this course cadmium estimations in blood and urine should be made. This routine can be repeated until the patient becomes free of cadmium. In the three cases quoted there was rapid response to the chelating agent. The cadmium ion replaces the calcium ion in the chelating agent. The cadmium is excreted by the kidneys as a non-irritating chelate. No unpleasant side-reactions occurred (Cotter, 1958).

SUMMARY

A case of acute cadmium poisoning due to cutting scrap metal with a welder's torch is described. Subsequent investigation following the recognition of symptoms of cadmium poisoning revealed that included among the scrap were some sections which had been coated with a protective finish containing cadmium. The industrial hazards of using cadmium without taking the necessary precautions are discussed. The commoner uses of the metal are also given.

I thank the United Kingdom Atomic Energy Authority for permission to publish this paper, and Dr. J. B. Lynch, Mr. J. M. High, and Mr. S. W. Maxted for reading and making helpful comments on this paper.

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" It is little appreciated by medical men as well as laymen that the pattern of infectious disease in the community is constantly changing. The important disease of one period disappears to be replaced by another, which was once important. The rise in poliomyelitis is a good example ; for some 30–40 years ago it was an infection of little relevance to the community. It is a matter of great regret that the Staphylococcus has in the past been regarded as an unimportant organism for this must explain the fact that the steps to deal with what is now a redoubtable pathogen have not included the obvious one that the infectious disease hospital is the place in which the severe examples should be treated." (*Annual Report on the Work of the Infectious Diseases Hospitals, 1959.* Western Regional Hospital Board.)

Reviews

CLINICAL USE OF RADIOISOTOPES

Radioactive Isotopes in Clinical Practice. By Edith H. Quimby, Sc.D., Sergei Feitelberg, M.D., and Solomon Silver, M.D. (Pp. 451; illustrated. 75s.) London: Henry Kimpton. 1958.

Radioisotope Techniques in Clinical Research and Diagnosis. By N. Veall, B.Sc., F.Inst.P., and H. Vetter, M.D. (Pp. 417 +xii; illustrated. 50s.) London: Butterworth and Co. Ltd. 1958.

The clinical applications of radioactive isotopes continue to increase in scope and variety. Fortunately, even if rather belatedly, a number of authoritative textbooks on this subject have appeared and now cover most aspects of this field well. It would be difficult for any single work to be both comprehensive and thorough on so large a subject, but both the books under review deal excellently with important parts of the field as a whole.

Although a detailed knowledge of nuclear physics or of counting methods and equipment may be unnecessary to the clinical use of radioisotopes, there are many aspects of radiation physics with which some familiarity is of the greatest value to those wishing either to understand the basis of existing techniques or to apply them to new problems. It is this need that is met particularly well by the first two parts of *Radioactive Isotopes in Clinical Practice*, of which Part I, on "Basic Physics," is by Dr. Quimby, and Part II, on "Instrumentation and Laboratory Methods," is by Dr. Feitelberg. Dr. Quimby deals with a great amount of useful and relevant information in the lucid and succinct manner that readers of her work would expect. Dr. Feitelberg's section deals with the scope and basis of various counting methods in a thoughtful way which should prove particularly helpful in the selection or adaptation of equipment for the study of new problems. Criticisms of these sections are very minor: for example, that iodine 132 is not discussed even when referring to tests on children; that the possibilities of whole-body profile counting are not mentioned; or that the biological half-life of radioiodine in the thyroid does not in fact, as stated, give a direct indication of the turnover of the element, owing to the recirculation of isotope in the gland.

The third section, by Dr. Silver, is—within its scope—as valuable as the first two, although only the applications of radioiodine are dealt with in any detail. These chapters give sound and comprehensive accounts of the diagnostic and therapeutic value of this isotope, and the bibliographies are large and excellent. Criticisms are again trivial: that the study of congenital cretins might now be discussed more fully, that ^{132}I is only very briefly surveyed, and that the "only two reported cases" of leukaemia following radioiodine treatment of hyperthyroidism are different ones on pages 331 and 337. The review of isotopes other than radioiodine occupies only 70 pages, but mentions a substantial number of applications within this space. For its clear and comprehensive analysis of the basis of isotope applications in general, and of radioiodine in particular, this book is outstandingly important.

Veall and Vetter's *Radioisotope Techniques* is a book of comparable value and authority, and has in some respects a wider scope and a rather greater practical value to the clinician concerned with these procedures. The physical and counting methods are discussed in a realistic manner, and illustrated in terms of equipment, isotopes, and specific activities available, with good sections on chromatography, multiple tracer techniques, labelling of compounds, multicompartment analysis, and the behaviour of counters. The ensuing survey of the application of radioisotopes to clinical problems is outstandingly valuable, both for its clear and practical descriptions and for the unusually comprehensive survey of a wide variety of techniques with different isotopes. As the title indicates, the therapeutic uses of these materials are not included (apart from a brief final chapter), but the text deals very fully with diagnostic and experimental applications. Studies of local circulation, cardiac output, exchangeable electrolyte determinations, fat absorption, protein katabolism, thyroid function and localization, erythrocyte survival, vitamin-B_{12} absorption, placental circulation, liver blood-flow, and iron metabolism are described in a way that makes both the basis and the application of the methods clearly understandable. Apart from its good and helpful review of basic principles and theory, it is as a practical manual of a very wide variety of radioisotope techniques that Veall and Vetter's book will be of particular value.

E. ERIC POCHIN.

A DOPE FOR FAT DOGS

The Amphetamines. Their Actions and Uses. By Chauncey D. Leake, Ph.D. (Pp. 167+xv. 34s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

A huge literature has grown up on the amphetamines, including the British book on their clinical use by Howells, Betts, and Macdonald. The present publication is a monograph in a series of American lectures on pharmacology edited by the professor of pharmacology in the Ohio State University. It deals in a clear way with the physico-chemical properties of the amphetamines, their pharmacology, their therapeutic uses, and their sociological repercussions.

The book is easy to read by those who are not allergic to that type of American-English which never uses one word where two will do, or a simple expression where a florid one can be substituted. It is not so much a critical review of the pharmacological action of the amphetamines or of their clinical use as an apologia for their widespread prescription: "The wise physician who understands the actions of the amphetamines may use them with great success in an enormous variety of clinical conditions. These include depressed states, narcolepsy, post-encephalitic Parkinsonism, barbiturate poisoning, drug addiction and alcoholism, some behaviour problems in childhood, enuresis, a variety of psychopathic states and certain mental disorders of the aged, post-operative debility, obesity, the vomiting of pregnancy, and as an antidote to the hypnotic effects of anticonvulsant drugs"; amphetamines are also recommended in the house-breaking of dogs and cats and in the repulsive obesity of such pets which the oversolicitude of their masters and mistresses is apt to produce. The problem of addiction, habituation, and tolerance to the amphetamines is minimized: "all the

evidence indicates . . . that under the circumstances of their use by millions of people the occasional reports of possible habituation or untoward reaction are extremely insignificant." The amphetamines are described as "slightly more powerful in their pharmacological effect than caffeine": perhaps, then, the public's indignation over the use of these drugs to dope racehorses is slightly ridiculous when no one would be shocked by the poor beasts being given a drink of coffee.

With much of the book I profoundly disagree, but the author points out that "the whole matter of the possibility of addiction from any drug is a highly emotionally-charged subject . . . and offers an opportunity for publicity seekers, whether professional journalists or writers or professional scientists or physicians, to win public interest and attention." Perhaps I am one of these.

D. M. DUNLOP.

ADLER SYSTEMATIZED

The Individual Psychology of Alfred Adler. A Systematic Presentation in Selections from his Writings. Edited and annotated by Heinz L. Ansbacher, Ph.D, and Rowena R. Ansbacher, Ph.D. (Pp. 503+xxiii. 30s.) London: George Allen and Unwin Ltd. 1958.

Alfred Adler was less fortunate than Freud in the way in which his doctrines were propagated during his lifetime. While the psycho-analytic movement was from the outset well served by chroniclers, translators, and apologists of great literary ability, individual psychology was spread mainly by Adler's own ability as a lecturer and his capacity to put his theories into plain words to a predominantly lay audience. His own writings, while very clearly written, did not appear in a systematic way, so that his influence was more on the climate of psychopathological opinion in his time than on its literature. In the last ten years, however, a number of first-class accounts of individual psychology have appeared, notably those of Way and of Brachfield, so that the importance of Adler's work and the extent to which neo-Freudian concepts are recapitulations and modifications of his ideas is now being fully realized. Adler's writings cover the period from 1907 to his death in 1937. Many of them are difficult of access, and it is his very readable popular books that are best known. Because of the evil work of some of his translators and the extreme literalness with which many of his followers took his words, his work has not had full opportunities to speak for itself.

The primary aim of the authors has been to present individual psychology in Adler's own words and to supply a running commentary which relates it to other views both contemporary and subsequent. In order to achieve this they have wisely ignored the chronological order of his publications and have classified his work by topics. This has had the effect of systematizing it in a way which Adler himself never achieved. It has the effect, too, of demonstrating that Adler's original mind started off trains of thought which have undergone development in other minds working in quite different contexts. After a preliminary statement of general principles and of the relation of the Adlerian to other systems, the exposition is made by means of a series of extracts which deal with the development of personality, the individual's fictional conception of his goals in life, the striving for superiority, the importance of the drive to social adaptation, the "style of life" and the neurotic disposition, as well as the application of these concepts not only to neurosis but to the upbringing of children, to the prevention of crime, and to the sick community in its various forms. It is unfortunate that some of these concepts have rather inapt names as the result of poor translation, but as they now are so familiar it is too late to rename them. Throughout the book Adler's attitude to his patients and his subjectivist humanist approach become evident as a continuous narrative which is interesting enough even to make the reader impatient at times with the meticulous commentary which links the extracts.

The relationship of individual psychology to psychoanalysis, from which it takes its origin, is carefully set out, possibly with too much emphasis on differences rather than similarities. The discussion of masculine protest, on which Freud and Adler were irreconcilable, is seen to be the focal point of these differences, though the fact that the two men went their separate ways was as much a matter of personalities as psychologies. The authors have carried out at great pains a valuable and necessary task, for Adler's work is still bearing fruit, especially in the fields of psychosomatic medicine and social psychiatry.

ALEXANDER KENNEDY.

THE EMOTIONS AND TUBERCULOSIS

Emotional Factors in Pulmonary Tuberculosis. An Evaluation of Psychological Factors in Onset and Relapse and their Significance in Management, Treatment, and Prevention. By David M. Kissen. (Pp. 246+xvii. 35s.) London: Tavistock Publications, Ltd. 1958.

No one who has studied patients suffering from pulmonary tuberculosis can fail to be impressed by the frequency with which emotional upsets precede the onset of the disease. Much has already been written about the psychosomatic aspects of tuberculosis, but so far conclusions have been drawn from clinical impressions and have lacked a scientific basis. Dr. Kissen has made a praiseworthy attempt to study this problem statistically by comparing tuberculous patients with a control series of non-tuberculous patients attending the same chest clinic. Two investigations concerned emotional factors preceding the onset of tuberculosis and those preceding relapse. In both these studies he found a significant correlation between a break or threatened break in a love link—particularly one involving a romance, engagement, or marriage—and the development of active tuberculosis. The figures here are convincing, and this is perhaps the first time that the influence of emotional factors in the development of pulmonary tuberculosis has been convincingly demonstrated.

In the third investigation, however, the author is on less sure ground. It concerns the influence of personality traits, and 100% of the tuberculous patients are said to have an "inordinate need of affection," the importance of which has been stressed by Wittkower. But the assessment of such a common trait is highly subjective, and it is surprising that it was found in no more than 16% of the controls. It is difficult to accept the far-reaching conclusions which the author draws from this part of his work.

More than half the book is devoted to a review of the literature, followed by a long discussion relating the author's findings to psychosomatic aspects of tuberculosis and other diseases. The final section, which concerns the application of these findings to the

management of tuberculosis, is disappointingly short and indefinite. Merely to state that in certain circumstances psychotherapy may be of value conveys little to the physician who is not a trained psychotherapist but who wishes to treat his patient himself.

Nevertheless this book will enable all those concerned with tuberculosis to understand their patients better. Although chemotherapy has modified treatment and improved prognosis to such an extent that patients are subjected to far fewer emotional stresses than formerly, cure may well produce its own problems. One of Dr. Kissen's most interesting observations is that certain psychosomatic affections, particularly peptic ulcer and neurosis, occur significantly more frequently in patients who have recovered from pulmonary tuberculosis. Thus, when tuberculosis is providing the patient with a convenient escape from reality, its cure by modern methods may merely leave the house swept and garnished ready for occupation by other devils worse than the first.

A. F. FOSTER-CARTER.

EPILEPSY

Convulsive Disorders of Children. By Dora Hsi-Chih Chao, M.D., Ralph Druckman, M.D., and Peter Kellaway, A.M., Ph.D. (Pp. 151+vi; illustrated. 42s.) Philadelphia, London: W. B. Saunders Company. 1958.

This is a simple handbook, originally written for the staff of a children's clinic in Texas by three authors well informed in their subject. It presents in condensed form what we know to-day about the basis of epilepsy, and in a liberal way recognizes the importance of considering the child and his problems as well as his fits. Each short chapter is a judicious statement of one aspect of epilepsy, with a few selected references. The place of investigation and operation is discussed in a reasonable and carefully balanced way, and distinction is made between the more benign disorders—such as, for instance, the solitary convulsion, febrile convulsions, and breath-holding attacks. It is a useful guide for the practitioner.

DENIS WILLIAMS.

A FRENCH TAILPIECE

Traité de Médecine. Volume XVIII. *Mises au Point,* 1958. (Pp. 916+x; illustrated. 8,000 fr., bound 9,000 fr.) Paris: Masson et Cie. 1958.

The *Traité de Médecine* is a system of medicine in 17 volumes which has been designed and completed over the last nine years. An eighteenth volume has now been added to fill up gaps in the previous scheme and bring the series up to date. Whereas the preceding volumes have dealt with the separate systems, this one ranges over the whole field, though the chapters are grouped to show how they supplement the existing volumes. Nearly half the book is devoted to infections of one kind and another. Systems of medicine on this scale belong to a time when the rate of advance of medicine was slower than it is to-day. We now have to think of medical publications as dispatches from a moving front and not as records of a campaign that is static or ended. The present volume can be glanced through with interest as a picture of medicine from the French point of view, but it is a tailpiece rather than an independent survey of recent advances in medicine.

L. J. WITTS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Fear, Punishment, Anxiety and the Wolfenden Report. By Charles Berg. (Pp. 126. 20s.) London: George Allen and Unwin Ltd. 1959.

Clinical Chemical Pathology. By C. H. Gray, D.Sc., M.D., F.R.C.P., M.R.C.S., F.R.I.C. Second edition. (Pp 160+vii 14s.) London: Edward Arnold (Publishers) Ltd. 1959.

Synopsis of Gynecol gy. By Robert James Crossen, M.D., Daniel Winston Beacham, M.D., and Woodard Davis Beacham, M.D. Fifth edition. (Pp. 340; illustrated. 48s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

The Operation of Sterilising Autoclaves. A Symposium held at Brighton Technical College, School of Pharmacy, on May 9, 1959. (Pp. 45; illustrated. 7s. 6d.) London: Pharmaceutical Press. 1959.

Histologie und Mikroskopische Anatomie des Menschen. By Dr. W. Bargmann. (Pp. 820+xvi; illustrated. DM. 69.90.) Third edition. Stuttgart: Georg Thieme Verlag. 1959.

Prenatal and Paranatal Factors in the Development of Childhood Reading Disorders. By Ali A. Kawi and Benjamin Pasamanick. (Pp. 80. $3.) Lafayette, Indiana: Society for Research in Child Development, Inc. 1959.

The Cytology of Inflammatory Exudate: A Study on Normal Subjects and on Patients Showing Quantitative or Qualitative Changes of the White Blood Picture. By Povl Riis. Translated from the Danish by Anna la Cour. (Pp. 268; illustrated. Dan. kr. 38.) Copenhagen: Munksgaard. 1959.

Care of the Aged in Norway. By Finn Danielsen. (Pp. 56: illustrated. 6s.) Oslo: Norwegian Joint Committee on International Social Policy. London: Bailey Bros. and Swinfen, Ltd. 1959.

Le Laryngologiste et les Données Actuelles du Traitement des Insurrisances Respiratoires Aigues. By Paul Aboulker, with the assistance of J. Lissac and O. Saint-Paul. (Pp. 512; illustrated. 6,000 fr.) Paris: Librairie Arnette. 1959.

Report of the First Institute on Clinical Teaching. Edited by Helen Hofer Gee and Julius B. Richmond, with the assistance of the Planning Committee. Editorial co-ordination by E. Shepley Nourse. Part 2. (Pp. 233+xxx.) Evanston, Illinois: Association of American Medical Colleges. 1959.

The Physiology and Treatment of Peptic Ulcer. Edited by J. Garrott Allen with 11 Contributors. (Pp. 236+x; illustrated. 56s. 6d.) Chicago: University of Chicago Press. London: Cambridge University Press. 1959.

Human Biochemical Genetics. By H. Harris. (Pp. 310+viii; illustrated. 37s. 6d.) London: Cambridge University Press. 1959.

Einführung in die Bakteriologische Diagnostik. Ein Leitfaden für das kleine Laboratorium. By J. Lindenmann. (Pp. 120+iv; illustrated. Sw. fr. 24.) Basle, New York: S. Karger. 1960.

The Mother-Child Interaction in Psychosomatic Disorders. By Ann M. Garner and Charles Wenar, with Jennie B. Kahn and Jean P. Chapman. (Pp. 290+viii. $6.) Urbana, Illinois: University of Illinois Press. 1959.

Biopsy Manual. By James D. Hardy, M.D., James C. Griffin, Jr., M.D., and Jorge A. Rodriguez, M.D. (Pp. 150+xii; illustrated. 45s. 6d.) Philadelphia and London: W. B. Saunders Company. 1959.

Handbook of Circulation. Analysis and Compilation by Philip L. Altman. Edited by Dorothy S. Dittmer and Rudolph M. Grebe. (Pp. 393+xv. 52s.) Philadelphia and London: W. B. Saunders Company. 1959.

Metabolic Care of the Surgical Patient. By Francis D. Moore, M.D. Illustrated by Mildred Codding, A.B., M.A. (Pp. 1,011+x. £7.) Philadelphia and London: W. B. Saunders Company. 1959.

Fundamentals of Gynecology. By Samuel J. Behrman, M.B., Ch.B., M.S., M.R.C.O.G.(Lond.), F.A.C.S., and John R. G. Gosling, M.D. (Pp. 416+xii; illustrated. 76s.) New York, London: Oxford University Press. 1959.

Recent Neurological Research. Edited by A. Biemond *et al.* (Pp. 330+viii; illustrated. 47s. 6d.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. 1959.

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NEW DRUGS FOR DEPRESSION

Despite all the advances in psychiatric treatment in the last twenty-five years there is still a mounting toll of over 5,000 successful suicides a year in England, and the number of unsuccessful attempts is much greater. Many of these are patients with depressive illnesses which have been wrongly diagnosed or unsuccessfully treated by both general practitioners and specialists alike. With the enormous additional burden of ill-health and misery brought about by lesser degrees of depressive illness, it is little wonder that the search for simple biochemical treatments has for many years been one of the aims of psychiatrists with a physiological bent. And the pharmaceutical manufacturers have also been aware for a long time that any drug helping depressive states will produce very material rewards.

Nearly twenty-five years ago S. A. Peoples and E. Guttmann[1] reported the euphoric effects of "benzedrine," and great hopes were aroused. But the amphetamines have been able to play only a very limited role in the treatment of depressions, helping most patients for only a day or two before relapse occurs. However, preparations combining small doses of the amphetamines with barbiturates have more recently won a place in the treatment of milder depressions, though a tendency to cause addiction is a worrying feature.

After the publication of some observations on the euphoric effects of iproniazid ("marsilid") in patients being treated with this drug for tuberculosis, H. P. Loomer, J. C. Saunders, and N. S. Kline[2] in 1957 reported on its value as a "psychic energizer" in mentally ill patients. It has since become obvious that this drug—and a whole range of others having a common action as inhibitors of amine oxidases[3]—can be most beneficial in certain states of depression. Recently the *Annals of the New York Academy of Sciences* published a volume[4] of nearly 500 pages containing the series of papers given at a special conference on these amine-oxidase inhibitors in New York in November, 1958. Four months later a conference was also held at McGill University on "Depressions and Allied States," and the *Canadian Psychiatric Journal* has published a special supplement[5] on it in which much space is devoted to discussion of yet another new drug, imipramine ("tofranil"), now being used widely in the treatment of depression in both Europe and America. Imipramine is, however, quite a different type of drug, more resembling chlorpromazine in its chemical structure than any of the amine-oxidase inhibitors.

So far comparatively little work has been published in Great Britain on these two groups of remedies. But this has not stopped manufacturers from indulging in intensive advertising here to try to persuade general practitioners, physicians, and psychiatrists to use these drugs. P. J. Dally and W. Sargant[6] recently drew attention in this *Journal* to their dangers if used too frequently by doctors who have only a manufacturer's over-enthusiastic leaflets as their guide to therapy. They predicted, for instance, that avoidable suicides would occur if the statements of some manufacturers that their preparations were as good as, and could replace, electroconvulsion therapy (E.C.T.) were taken too literally and severely depressed patients were treated with them for too long before being referred for convulsion therapy.

What, then, is the present position of these new drugs in relation to that of other treatments of depression such as E.C.T.? British contributions to this problem, though small, will probably prove to have been valuable. For instance, E. West and P. J. Dally[7] have differentiated a group of "atypical" or "hysterical" depressions, sometimes resembling anxiety hysteria and occurring in good previous personalities, which seem to be specifically helped by iproniazid while doing badly with E.C.T. At the New York conference L. Alexander and A. W. Berkeley[8] independently reported a similar finding; they have also tried to pinpoint those neurotically depressed patients who may be helped by the amine-oxidase inhibitors, describing some of the characteristic complaints of their group as "inability to do anything—to work or even to go out of the house—fatigue, exhaustion, listlessness, not feeling well, unhappiness, being 'down,' inability to eat, diffidence, and lack of self-confidence."

Many contributors at this conference discussed the value of iproniazid and other amine-oxidase inhibitors in the more endogenous types of depression, but here there were divergences of opinion. Some were more insistent than others that

[1] Peoples, S. A., and Guttmann, E., *Lancet*, 1936, **1**, 1107.
[2] Loomer, H. P., Saunders, J. C., and Kline, N. S., *Psychiat. Res. Rep. Amer. psychiat. Ass.*, 1957, **8**, 129.
[3] See *Brit. med. J.*, 1959, **2**, 1238.
[4] "Amine Oxidase Inhibitors," *Ann. N.Y. Acad. Sci.*, 1959, **80**, 551.
[5] "McGill University Conference on Depression and Allied States," *Canad. psychiat. Ass. J.*, 1959, **4**, Special Supplement.
[6] Dally, P. J., and Sargant, W., *Brit. med. J.*, 1959, **2**, 1481.
[7] West, E., and Dally, P. J., ibid., 1959, **1**, 1491.
[8] Alexander, L., and Berkeley, A. W., *Ann. N.Y. Acad. Sci.*, 1959, **80**, 669.
[9] Ball, J. R. B., and Kiloh, L. G., *Brit. med. J.*, 1959, **2**, 1052.

endogenous depressions could be helped almost as readily as neurotic ones. Most participants agreed, however, that E.C.T. was still needed to help many endogenously depressed patients. Alexander and Berkeley, for instance, found that, while the recovery rate in their group of neurotically depressed patients treated with iproniazid was as high as 88% (to achieve such a figure it is almost certainly necessary for the patients in the group to have had a good personality prior to the onset of the symptoms), only 26% of their patients with severe endogenous depressions were greatly helped. Dally and Sargant also insist, despite their intensive use of antidepressant drugs, that E.C.T. is still needed in the treatment of a large number of depressions. At the New York conference, however, there were very hopeful reports that these drugs may be able to reduce the number of electroconvulsive treatments needed in some courses, that recurrent attacks of depression had sometimes been stopped by their use, and that they had even helped some endogenous depressive states where E.C.T. had failed.

Since iproniazid can cause a dangerous and sometimes fatal jaundice in up to 1 in 250 patients treated by it, the search for other amine-oxidase inhibitors which it is hoped will be safer has been intensive. In Britain there are now three of these on the market, phenelzine ("nardil"), nialamide ("niamid"), and phenylisopropyl hydrazide ("cavodil"). Isocarboxazid ("marplan") should also become available soon. Various contributors to the New York conference confirmed that phenelzine, isocarboxazid, and phenylisopropyl hydrazide can all be used as substitutes for iproniazid. In England, also, Dally and Sargant have found that though nialamide was not effective as a substitute for iproniazid the other three drugs were. As none of them may be found to be as good as iproniazid in all patients, alternatives should be tried in resistant cases. No toxic hepatitis has so far been reported with either phenelzine or isocarboxazid, but a death from jaundice has occurred with phenylisopropyl hydrazide in the U.S.A.

The amine-oxidase inhibitors, unfortunately, can cause hypotension as another complication: this may be shown by giddiness, swimming feelings in the head, and even states of temporary vasomotor collapse with marked falls in the blood-pressure. These can generally be overcome by an appropriate lowering of the dose, but it should not be forgotten that the effects of these drugs can be cumulative and that the side-effects can take some days to clear up after their use is stopped.

As to the use of imipramine ("tofranil"), there seems to be agreement with the conclusion of Ball and Kiloh[9] that this is of greater value in the more endogenous states of depression, though it also helps neurotic depressions. It is a more expensive drug to use than the amine-oxidase inhibitors and may take longer to act. Sometimes it is most effective when given intramuscularly for several days, and up to two or three weeks may be needed before a severe endogenous depression shows a satisfactory response. The dosage, which may have to be large, must be carefully adjusted to each patient. Again, at the end of a course of treatment, a high proportion of patients will be found not to have been helped but who will still do well with E.C.T. If E.C.T. is readily available the best plan is often to give the patients with more severe depressions a few electroconvulsive treatments together with imipramine or one of the amine-oxidase inhibitors, and then try to maintain recovery with these drugs after E.C.T. has been stopped.

Some anergic types of schizophrenia are reported to have been improved by the amine-oxidase inhibitors, but the risk of causing a dangerous flare-up of acute schizophrenic symptoms in other patients is very real with both groups of drugs, especially if the correct diagnosis has been missed in an already agitated patient. Here again suicide may be precipitated. Both groups of drugs can also induce states of hypomania in depressed patients: if that happens, then these drugs should be stopped immediately and tranquillizers such as chlorpromazine given instead.

The new drugs now being used in the treatment of depression have shown great promise, which, it is much to be hoped, will not become obscured because of over-enthusiastic and misleading advertising or of indiscriminate use before all their potentialities and very real dangers have been better worked out in Britain.

CAUSES OF "DUMPING"

The surgical treatment of peptic ulceration is still the subject of discussion and dispute. There are two contestants for supremacy—gastrectomy, and vagotomy with gastro-enterostomy. Each has its disadvantages. Which of the two is the more effective in preventing recurrent ulceration cannot be decided at present. No firm conclusion can be reached until the results of properly conducted clinical trials have been assessed on patients who have been observed for twenty years after operation. The final results of several trials begun soon after the last war will not be available for a few years. At present gastrectomy has the lower recurrence rate, but only by a narrow margin. It is therefore the

complications of the two operations which tend to influence the surgeon's choice. Each has one major disadvantage: vagotomy is sometimes followed by persistent and embarrassing diarrhoea; gastrectomy may have as its sequel the complication aptly if inelegantly called "dumping."

Dumping was first described in the early part of the century as a sequel of simple gastro-enterostomy, but it does not often complicate this operation. Clinically it has two facets; one resembles peripheral vascular collapse with symptoms of weakness, fainting, palpitation, tachycardia, and sweating. The other is made up of alimentary symptoms—nausea, colic, and diarrhoea. It was shown[1] that symptoms could be readily produced by drinking solutions of high osmotic pressure such as those with a high content of sugar or salt, and it was suggested that these constituted an unusual stimulus to the jejunal mucosa, which is normally protected by the reservoir action of the stomach. At first it was thought[2] that jejunal spasm was the cause of the whole symptom complex, which would readily account for the colic and diarrhoea. However, though jejunal spasm induced by distending the jejunum with a balloon can cause dumping,[3,4] it does so in only just over 10% of patients suffering from the classical post-prandial symptoms.

The next suggestion[4] was that hyperosmotic solutions introduced suddenly into the jejunum cause such a rapid flow of jejunal secretion to occur that it is equivalent to a sudden drop in blood volume. The patient, in fact, puts himself into a mild state of shock with each meal. To support this contention, investigators[4,5] measured the change in plasma volume during the period of dumping symptoms. In a normal person the plasma volume decreases slightly after eating, but the changes are greater when a patient has had gastrectomy. In general, the greater the fall in plasma volume, the more intense the symptoms. But these results were not consistent enough to warrant the assumption that dumping is unquestionably caused by decrease in blood volume. In some cases a considerable drop was not associated with symptoms at all[5]; in others a minimal change in plasma volume was accompanied by severe symptoms.

L. P. Le Quesne, M. Hobsley, and B. H. Hand have studied this problem afresh, and report their results in the opening pages of the *Journal* this week. They set out not only to estimate changes in plasma volume but to discover why some patients have dumping symptoms with a given decrease in volume and others do not. By using the ingenious method of applying venous tourniquets round the thigh to simulate loss of blood,[6] they were able to show that those patients who experienced symptoms of dumping but who had a small decrease in plasma volume were sensitive to similar small changes produced by thigh tourniquets. Likewise, patients with large changes in plasma volume but who did not experience dumping were immune to the effects of thigh tourniquets. This attempt to rationalize the paradoxes associated with the explanation that changes in blood volume are the cause of dumping is ingenious, though the argument is still not quite conclusive. Results of other workers showing that dumping can occur without any significant change in plasma volume need explanation, as also does the fact that balloon distension alone can cause characteristic dumping. In a second article Hobsley and Le Quesne consider the possible methods by which a change in plasma volume could occur. They show that this change is directly proportional to the rate at which the blood sugar rises in the first ten minutes after oral ingestion of a standard glucose drink. One explanation of this is that, in the patient who experiences dumping, gastric emptying is rapid and therefore glucose will pass quickly into the jejunum and be absorbed rapidly. The authors take a bold leap, however, and suggest that the rapid rise in blood glucose is the cause of dumping instead of the effect. They argue that this quick rise in blood sugar interferes osmotically with the fluid shift across the jejunal epithelium, causing a greater and more rapid transfer of fluid into the lumen of the bowel. In order to account for the great variation in the frequency of dumping, they suggest that some people are metabolically different from others in that they do not metabolize blood glucose rapidly and therefore develop a high concentration shortly after ingesting a carbohydrate meal. To support this view they gave patients with dumping symptoms insulin in varying doses and found that the changes in plasma volume were significantly decreased as a result; they also found that dumping symptoms were diminished by the administration of insulin before a meal.

While it is too early yet to subscribe wholeheartedly to this original idea, it has its attractions. However, investigations have not shown directly that there is a rapid shift of fluid across the jejunal mucosa in patients who have had a gastrectomy; the evidence has been by inference from the change in plasma volume. This change could be due to pooling of blood in the venous system instead of actual loss of fluid across the bowel wall. If a high blood-sugar is one of the factors in inducing dumping,

[1] Machella, T. E., *Ann. Surg.*, 1949, **130**, 145.
[2] Glazebrook, A. J., and Welbourn, R. B., *Brit. J. Surg.*, 1952, **40**, 111.
[3] Goligher, J. C., and Riley, T. R., *Lancet*, 1952, **1**, 631.
[4] Butler, T. J., and Capper, W. M., *Brit. med. J.*, 1951, **1**, 1177.
[5] Peddie, G. H., Jordan, G. L., and De Bakey, M. E., *Ann. Surg.*, 1957, **146**, 892.
[6] McMichael, J., and Sharpey-Schafer, E. P., *Brit. Heart J.*, 1944, **6**, 33.

it could be reproduced experimentally, in those patients who did not get symptoms, by intravenous administration of glucose at the same time as the meal was taken. There is still much work to be done before the fluid-shift theory can be accepted without question as the cause of dumping; and more evidence is required to show what part carbohydrate metabolism may play. Meanwhile further contributions from these authors on this important subject are awaited with interest.

There are a few practical steps which may be taken to prevent or diminish dumping. The incidence is less after a Billroth I gastrectomy than after a Polya type; moreover, it is less after the Polya operation if a narrow stoma is made. If symptoms are incapacitating after a Polya gastrectomy, it may be justifiable to convert it to a Billroth I, though this is by no means always successful. A patient who experiences symptoms after operation should be reassured that they will disappear, as only 5% are affected after two years. He will gain relief if he lies down when taking his meals and if he takes fluid between instead of during them. No drugs influence the symptoms in any way.

APATHETIC HYPERTHYROIDISM

The diagnosis of classical hyperthyroidism is usually self-evident. But the disease can present in unusual guises or *formes frustes*, in which the clinical picture is not fully developed; especially is this so in older patients. Chvostek[1] in 1917 drew attention to these cases, long recognized by earlier authors such as Marie and Charcot. He stressed in particular what he termed "monosymptomatic hyperthyroidism" in which symptoms were predominantly cardiovascular or neurological. In 1930 W. W. Hamburger and M. W. Lev[2] described five cases of thyrotoxicosis masked by prominent gastro-intestinal symptoms and displaying an unusual degree of apathy.

Most authorities would agree that restlessness with rapid or hyperkinetic movements, rather than apathy, constitutes a cardinal feature of thyrotoxicosis. Hyperkinesis as a sign has been stressed by E. J. Wayne[3] and is allotted a high score among the "weighting factors" on which J. Crooks, I. P. C. Murray, and Wayne[4] base their clinical diagnostic index of thyrotoxicosis and which Professor Wayne described in his Lumleian Lecture published in this *Journal* a fortnight ago. That there are exceptions to the rule was first noted by F. H. Lahey in 1931,[5 6] when he described patients with "apathetic thyroidism" whose behaviour contrasted with the usual "activated" or hyperkinetic demeanour of thyrotoxic patients. Lahey emphasized that this was an unusual but distinct type of reaction to the disease. Clinically, the apathetic patients were middle-aged or elderly, mainly women; eye signs were slight or absent, and there was little enlargement of the thyroid gland. The patients looked older than their years, with dry wrinkled skin, and showed few signs of disease in the circulatory system. Loss of weight was greater than usual owing to long delay in recognition of the thyrotoxic state. Death occurred in stupor or coma without the frantic agitation of a thyrotoxic storm; operation on the thyroid gland was fraught with a high mortality. In Lahey's own words, these patients often "either never awaken from their anaesthetic or awaken only to sink comfortably, leisurely, without activation, into semistupor, or to become completely unconscious and die peacefully with practically none of those gruesome activation signs which accompany death with typical activation thyroidism."

Since Lahey's account many cases of "masked" hyperthyroidism have been published but few detailed reports of the apathetic form of the disease.[2 7-9] Recently R. R. McGee and colleagues[10] reviewed the literature and described four patients with Graves's disease in whom apathy of varying degree, at one stage or another, was a prominent feature, though in the strict sense these were not "masked" cases.

There has been little speculation on the cause of apathy in these rare types of the disease, and virtually no clinical investigation into it. Of special interest, therefore, is the finding of W. R. Brewster and colleagues[11] that most of the physiological signs of thyrotoxicosis in dogs can be abolished by total sympathetic blockade. This procedure brings back to normal the oxygen consumption, heart rate, and circulatory signs, suggesting that the response to hyperthyroidism may be mediated through the sympathico-adrenal hormones, augmented by thyroxine. In man W. F. Diller and R. Kilpatrick[12] have shown that the urinary excretion of adrenaline is greatly raised in hyperthyroidism in parallel with the severity of the disease, and J. J. Canary and colleagues[13] have reported a striking symptomatic and objective improvement in hyperthyroid patients given large doses of reserpine; some, indeed, were converted from a hyperkinetic to an apathetic state. The levels of protein-bound iodine in the plasma and of uptake of radio-iodine did not change, though there was some fall in basal metabolic rate. To account for this action of reserpine, Canary and colleagues[13] have suggested blockade of the sympathetic centres in the diencephalon. Lastly, there is experimental evidence in animals that thyrotoxicosis induced by giving thyroxine may lead ultimately to exhaustion of the adrenal cortex.[14 15] As McGee and

[1] Chvostek, F., *Morbus Basedowi und die Hyperthyreosen*, 1917, Berlin.
[2] Hamburger, W. W., and Lev, M. W., *J. Amer. med. Ass.*, 1930, **94**, 2050.
[3] Wayne, E. J., *Brit. med. J.*, 1954, **1**, 411.
[4] Crooks, J., Murray, I. P. C., and Wayne, E. J., *Quart. J. Med.*, 1959, **28**, 211.
[5] Lahey, F. H., *Ann. Surg.*, 1931, **93**, 1026.
[6] —— *New Engl. J. Med.*, 1931, **204**, 747.
[7] Wohl, M. G., *Med. Clin. N. Amer.*, 1933, **17**, 751.
[8] McMillan, T. M., and Wendkos, M., *Int. Clin.*, 1937, **3**, 213.
[9] Hare, L., and Ritchey, J. O., *Ann. intern. Med.*, 1946, **24**, 634.
[10] McGee, R. R., Whittaker, M. D., and Tullis, I. F., ibid., 1959, **50**, 1418.
[11] Brewster, W. R., Jr., Isaacs, J. P., Osgood, P. F., and King, T. L., *Circulation*, 1956, **13**, 1.
[12] Diller, W. F., and Kilpatrick, R., *Brit. med. J.*, 1958, **2**, 823.
[13] Canary, J. J., Schaaf, M., Duffy, B. J., and Kyle, L. H., *New Engl. J. Med.*, 1957, **257**, 435.
[14] Deane, H. W., and Greep, R. O., *Endocrinology*, 1947, **41**, 243.
[15] Hoffmann, F., Hoffmann, E. J., and Talesnik, J., *J. Physiol. (Lond.)*, 1948, **107**, 251.

colleagues[10] point out, these findings may offer a clue to the cause of apathy in occasional patients with hyperthyroidism, the hypothesis being that there is a failure of the usual sympathetic, and perhaps also adrenocortical, response to increased secretion of thyroid hormone. Future measurements of urinary excretion of catecholamines in such cases may help to decide the issue.

WORKING CONDITIONS IN POTTERIES

The pottery industry in Stoke-on-Trent was chosen as the subject of the second of the pilot surveys of industrial health recommended by the Standing Industrial Health Advisory Committee of the Ministry of Labour and National Service. The first survey,[1] carried out in Halifax, brought to light much that was still unsatisfactory in working conditions, and the report[2] of the second survey, which was carried out by a team from H.M. Factory Inspectorate, also contains some disquieting information.

In 1956 the pottery industry in North Staffordshire employed 48,184 persons in 298 factories, of which only 63 had more than 250 workers. An important fact, not sufficiently emphasized in the report, is that approximately 60% of the employees are women, many of them married and of child-bearing age. The industry has long been indicted for its decrepit slum factories developed from a cottage system over the last 200 years.[3] For many years after the second world war the industry was prosperous, but it is again struggling against foreign competition and import quotas in overseas markets, and it is disappointing to learn from the report that in nearly half the factories there has been no reconstruction to speak of since 1938. Nevertheless there are a few excellent modern factories.

During the last 30 years there has been a substantial extension of firing by gas and electricity in tunnel ovens. This has diminished the smokiness of the Five Towns and relieved the oven-men of much hard physical labour and exposure to intense heat. A study of the environmental conditions in the potters' shops showed that temperatures up to 90° F. (32° C.) were not uncommon and that in one-sixth of the factories the room temperature was above the legal limit (in general 75° F. – 24° C.). Pneumoconiosis is still the most serious specific occupational disease, though some progress has been made in certain processes by the substitution of alumina for flint. The employers, the report states, are dust-conscious. Lead poisoning, once a very serious hazard, has been almost eliminated by the statutory prohibition of raw lead glazes and their replacement by leadless or low-solubility lead glazes. Dermatitis is a risk in some processes, and occasionally injury to health may arise from organic chemicals, hydrofluoric acid and other fluorine compounds, ceramic colours, and carbon monoxide.

Appointed factory doctors and the Pneumoconiosis Panel carry out the statutory services of medical inspection. Voluntary medical services arranged by the employers are practically non-existent; a few doctors work on a part-time basis, and altogether seven nurses were employed to supervise the first-aid arrangements in eight factories. Despite ample local facilities for training, there is a dearth of first-aid workers. The statutory regulations about first-aid boxes and mess-rooms, it was discovered, were being neglected in many factories.

The inspectors have given an excellent account of pottery manufacture and of environmental conditions in the industry. Their report, however, provides no vital statistics relating to the workers and their dependants—no figures throwing light on their general health or on the incidence of occupational and non-occupational disease. Nor is there any reference to such matters as the turnover of labour in the industry or to personnel management.

[1] *Industrial Health—A Survey in Halifax*, 1958, H.M.S.O., London. See *Brit. med. J.*, 1958, **1**, 764.
[2] *Industrial Health—A Survey of the Pottery Industry in Stoke-on-Trent*, 1959, H.M.S.O., London. Price 5s.
[3] *Reconstruction in the Pottery Industry*, 1945, Manchester.

PATHOLOGICAL LACTATION

The factors responsible for normal lactation are so dependent on the complicated hormonal changes peculiar to pregnancy and the puerperium that spontaneous milk production unrelated to the birth process is a rarity. But it does occur, and its incidence after the use of some recently introduced drugs has been described by several writers. The principal agents are the phenothiazine derivatives, reserpine, and various ganglion-blocking preparations. The first appears the most powerful in this respect, and S. Kulcsar *et al.*[1] noted galactorrhoea in every one of 300 psychiatric patients receiving 300–400 mg. of chlorpromazine daily for 10 days. When the dosage was halved the number affected fell to 10%. B. Robinson[2] found that the administration of 1–5 mg. of reserpine daily for four weeks caused milk to be secreted in 10% of his patients, and P. Abély[3] reports a similar incidence with tetra-ammonium sulphate. A coincidental finding in nearly all the patients was complete amenorrhoea. Hormonal assays gave normal figures for the 17-ketosteroids and follicle-stimulating hormones, but a marked depression in the oestrogen level was observed in all the cases. R. Neimeier *et al.*[4] have recently reviewed the subject and report four more personal cases.

The exact mechanism of this abnormal secretion is somewhat obscure. Physiological lactation is provoked by mechanical stimulation of the hormonally prepared breast in the presence of prolactin, and all three factors are essential for its production. The proliferative and secretory changes of pregnancy are the result of the high levels of the circulating oestrogen and progesterone at this time. Prolactin is an anterior-pituitary hormone which appears to attain its peak concentration at 40 weeks, and the mechanical factor provoking lactation is, of course, suckling. All three factors are, however, subject to pathological variation, and prolonged lactation, or lactation quite unassociated with pregnancy, may result from any one being affected.

[1] Kulcsar, S., *et al.*, *Presse. méd.*, 1957, **65**, 1288.
[2] Robinson, B., *Med. J. Aust.*, 1957, **11**, 239.
[3] Abély, P., *Ann. méd.-psychol.*, 1956, **114**, 591.
[4] Neimeier, R., *et al.*, *Schweiz. med. Wschr.*, 1959, **89**, 442.

Prolonged secretion caused by continued suckling may extend to years, and a similar condition may be initiated, quite independent of pregnancy, by masturbation of breast or nipple. In both types menstruation is normal and there are no gross hormonal variations. Hormone lack is seen in the Chiari-Frommel syndrome, in which prolonged post-partum lactation is associated with amenorrhoea, wasting, genital atrophy, and a marked diminution in the oestrogen concentration in the blood. An example of more direct hormonal influence is the secondary lactation associated with acromegaly, pituitary tumours, and chorionepithelioma.

The common denominator in all the non-mechanical cases of pathological lactation is a marked depression in oestrogen activity. How this inhibition occurs, is however, obscure, and the manner in which the drugs mentioned produce this bizarre syndrome of extra-parturient galactorrhoea is problematical. Their number and variation in chemical structure negative a specific anti-oestrogenic action; most probably secretion of milk is a selective hypothalamic response secondary to the depressing action of the drugs on the cerebral cortex. But, whatever the mechanism, lactation and amenorrhoea will result if the dosage is sufficiently high. Both symptoms are usually quickly reversed on cessation of treatment, but the fact that they can occur so easily calls for caution in the use of many of these at least potentially dangerous new drugs.

DOCTORS AND NATIONAL SERVICE

The call-up of doctors liable for national service will continue until the end of 1960. After that it is planned that compulsory recruitment will come to an end. The statement announcing this (published in the *Supplement* this week at p. 19) also warns that the demand for doctors in the Forces is likely to be heavy throughout 1960, a demand which will have to be met largely from doctors still liable for national service. Since none of those who become provisionally registered after January 1, 1960, and none of those whose deferment of call-up extends beyond the end of 1960 are likely to be needed except in an emergency, the pool from which doctors are to be recruited for national service is a contracting one, while, fortunately, the pool from which hospitals draw their junior medical staff should gradually expand.

The call-up of doctors for national service is now controlled by the Central Medical Recruitment Committee, the predecessor of which, the Central Medical War Committee of the B.M.A., was established soon after the beginning of the first world war and carried out the task of recruiting doctors for the Forces throughout the second world war as well. The Central Medical Recruitment Committees (one for England and Wales and one for Scotland), which were set up in 1952, are now committees of the whole profession, not just of the B.M.A., though the Association appoints many of the members and provides them with premises and staff. Most of the work of the C.M.R.C. is done through a large executive subcommittee which meets monthly, mainly to consider applications from young doctors for deferment of their national service. Because of the continuing need for doctors in the Forces and the reduced number eligible for conscription, the task of the committee in 1960 will be no less onerous than before, and just as thankless.

ROYAL COMMISSION REPORT

The Sunday newspapers seem to specialize in titbits for the medical profession. "A new deal for experienced family doctors and higher rewards for consultants and specialists, to encourage distinction in all branches of the profession, are expected to be among the chief recommendations of the Royal Commission under Sir Harry Pilkington, whose report . . . is now in its final form," writes the *Sunday Times'* political correspondent. The Commission, "it is confidently believed," will propose substantial changes in the present pay structure of the N.H.S. The profession, it is said, wants to know whether there may be a new scheme "to replace the present capitation system geared to the number of patients, and whether a practicable alternative is possible." There may be some form of merit awards for "senior and experienced general practitioners." The *Sunday Dispatch* says, quite simply, that the report is "expected to recommend the Government to grant them [40,000 N.H.S. doctors and their hospital colleagues] a £5-a-week increase."

Are these two newspaper reports guesswork or inspired leaks to the press? And why are they being given so much prominence some four weeks or so before the publication of the report of the Royal Commission on the Remuneration of Doctors and Dentists in the National Health Service?

"GUT"

A new specialist periodical will soon be added to the list of those published by the British Medical Association. For some years now there have been intermittent discussions with the British Society of Gastroenterology on the desirability of publishing a journal devoted to this subject. And now the decision has been taken. The new quarterly will go under the terse and brief title of *Gut*. This word is not only shorter, but more accurate for the purpose, than the Latin and Greek derivatives "abdomen" and "enteron." Its inspiration is not only embryological. Some of the most famous special journals have appeared under such titles as *Heart*, *Brain*, and *Blood*. But more important than the title will be the contents of the new journal. A strong editorial committee has been set up under the editorship of Mr. Harold Edwards, with Dr. F. Avery Jones as editorial secretary. The British Society of Gastroenterology has gone on from strength to strength, and there are in this branch of medicine, as in so many others, new developments arising out of new techniques, and out of the application of new knowledge in other fields to the study of the disorders of the gastrointestinal system: enough to justify a new journal.

It is hoped that the first issue of *Gut* will appear towards the end of March, and thereafter at quarterly intervals, at an annual subscription of £3. Orders should be sent to the Publishing Manager, *British Medical Journal*, B.M.A. House, Tavistock Square, London.

Drug Treatment of Disease

MALE SEX HORMONES

BY

P. M. F. BISHOP, D.M., F.R.C.P.

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Androgens for Therapeutic Use

The true male hormone, secreted by the Leydig cells of the testis, is *testosterone*. It is inactive when given by mouth; its effect is very transient if given by injection; and indeed it is useful as a therapeutic agent only when implanted in the form of 100-mg. pellets, which remain effective for about six months. Pellet implantation should be undertaken only with full aseptic technique. Though the procedure is simple it constitutes a minor operation, and therefore does not commend itself to the busy practitioner.

Androgens have three main properties. They promote the development of male secondary sex characters, they are "anti-oestrogenic," and they are anabolic.

The objectives in developing suitable derivatives of testosterone for therapeutic use are therefore to produce preparations that will promote male secondary sex characters and that are reasonably long-acting if given by injection or effective when administered orally; to find compounds that are "anti-oestrogenic" without giving rise to undesirable virilizing effects; and to elaborate substances which are principally anabolic rather than androgenic.

Esterification is the usual method of prolonging the activity of parenterally administered steroid compounds, and for many years *testosterone propionate* was the preparation employed for intramuscular injection. It remains effective for two to four days and should be given twice a week to maintain a constant action.

Though testosterone is practically inactive when given by mouth, the 17-methyl compound, *methyltestosterone*, is an efficient oral androgen. When given in the form of tablets to be swallowed, its absorption from the intestine and its passage via the portal circulation through the liver results in only a small proportion of the active principle eventually reaching the systemic circulation, so that this is an extravagant way of producing an androgenic effect. Methyltestosterone has therefore been prepared in the form of flat tablets which can be placed beneath the tongue or between the lip and the gum and slowly dissolved to allow the active principle to be absorbed directly into the submucous systemic vessels. Though administration of methyltestosterone is a wasteful method of producing purely androgenic effects, it is a convenient means of procuring "anti-oestrogenic" effects in various gynaecological conditions. Here dosage must be kept low to avoid virilizing side-effects, and fortunately low doses are usually effective in achieving "anti-oestrogenic" results. When used for such indications, therefore, the sublingual route would seem to be of little advantage.

NEW ANDROGEN COMPOUNDS

Long-acting Esters

A number of esters have been studied. These include *testosterone phenylpropionate* ("Tes.P.P."), which in doses of 50 mg. remains active for up to two weeks. *Testosterone oenanthate* ("primoteston depot") is about twice as potent as testosterone propionate, and an injection of 250 mg. remains effective for three to four weeks. Finally, a combination of esters of varying duration of activity is marketed under the trade name of "sustanon" in two doses, 100 mg. and 250 mg. The lower-dose ampoule contains 20 mg. of testosterone propionate, which comes into action immediately, its effect being taken over by 40 mg. of testosterone phenylpropionate for another week or ten days, when *testosterone isocaproate* (40 mg.) reaches its peak and remains effective for about another week. The 250 mg.-dose ampoule contains 30 mg. of the propionate, 60 mg. each of the phenylpropionate and isocaproate, and, in addition, 100 mg. of *testosterone decanoate*, which reaches its peak in two weeks and continues to be active for another two weeks. The lower-dose preparation should therefore be injected every two weeks and the higher-dose preparation every four weeks.

Another method of prolonging activity is to suspend the ester in solution in the form of microcrystals, and such a preparation is *testosterone isobutyrate* ("perandren M crystules") which is available in 50-mg. doses.

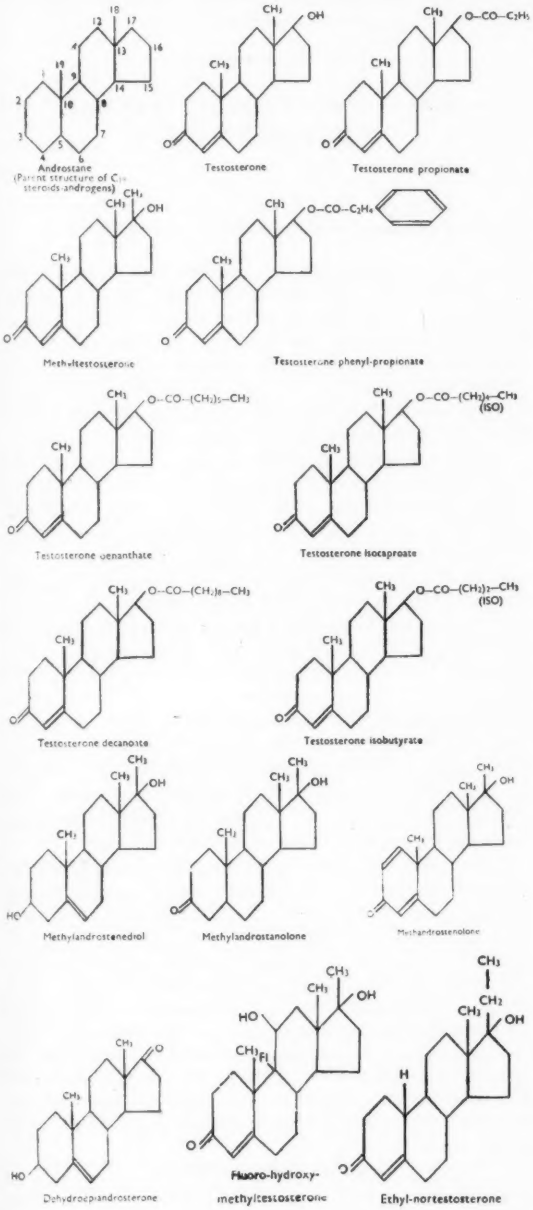
Orally Active Androgens

The tendency in recent times has been to search not for more potent orally active adrogens than methyltestosterone, but for substances with either powerful anti-oestrogenic or anabolic action which are at the same time weak androgens, so that they may be administered to women without fear of producing masculinizing side-effects. Two such compounds that have been available for some time are *methylandrostenediol* ("protandren," "stenediol") and *methylandrostanolone* ("androstalone," "anabolex"). When given in relatively small doses, such as 10 or 25 mg. daily, side-effects are seldom produced, but when high doses are employed, as in cases of inoperable carcinoma of the breast, virilization may occur. Another compound that has had a certain vogue among psychiatrists is the characteristic excretory product of adrenal androgens—namely, *dehydroepiandrosterone* ("diandrone").

The most recently introduced compounds are derivatives of 19-nortestosterone. Some are purely progestogenic, though their name suggests that they should be androgens. It should be remembered, however, that the orally active substitute for progesterone, ethisterone, is actually ethinyltestosterone. Two of these nortestosterone compounds are given for their relatively potent anabolic activity with little, if any, androgenic action. These are *19-nortestosterone phenylpropionate* ("durabolin") and *ethyl-nortestosterone*, or norethandrolone ("nilevar"). Both may be given by injection, durabolin in 25-mg. doses once a week, nilevar in 25- or 50-mg. doses daily or in tablet form in doses of 30 to 50 mg.

Another new preparation is a halogenated testosterone compound, *fluoro - hydroxy - methyltestosterone*, fluoxymesterone ("ultandren," "halotestin"), which is said to be five times as potent as methyltestosterone both as an androgen and as an anabolic agent. It is supplied in 1-mg. and 5-mg. tablets.

Yet another recent preparation is *methandrostenolone* ("dianabol"), which is claimed to be a powerful, orally effective, non-virilizing anabolic agent to be given initially in daily doses of 15 or 20 mg., the maintenance dose being 5 or 10 mg.



Structural formulae of androgens in therapeutic use.

Androgen Combinations

These are combinations of androgen with either oestrogen or progestogen. The former are advocated for use in treating menopausal symptoms, and each tablet consists of *methyltestosterone* 3 mg. and 0.01 mg. *ethinyloestradiol*. However, these combinations should be used with caution. Hirsutism can develop as the result of their prolonged and continuous use, especially when more than 3 tablets daily are prescribed. Another combination of androgen and oestrogen is *testosterone oenanthate* 65 mg. and *oestradiol valerianate* 4 mg. In this case the oestrogen is designed to counteract the possible virilizing effects of the long-acting androgen.

A combination of *methyltestosterone* 5 mg. and *ethisterone* 15 mg. has been prepared for use in menorrhagia.

INDICATIONS FOR ANDROGEN THERAPY

Replacement Therapy

Men suffering from gross androgenic deficiency leading to eunuchoidism, adult male castrates, and men showing evidence of pituitary failure owing to a chromophobe adenoma or craniopharyngioma may require androgen replacement therapy for the rest of their lives. In such circumstances it would seem logical to choose the most long-acting mode of administration, and this is pellet implantation. Six 100-mg. pellets of testosterone remain effective for six months.

If facilities for pellet implantation are not available, long-acting testosterone esters should be prescribed so that injections need be given as seldom as possible. Oral androgen therapy can be equally effective, but it is an extravagant way of giving androgens for life.

Anti-oestrogenic Therapy

Androgens may act in certain cases of functional menstrual disorders, such as menorrhagia and the premenstrual syndrome, either by directly antagonizing the effects of oestrogens or else by minimizing the results of oestrogen–progesterone imbalance during the post-ovulatory phase of the menstrual cycle. On the other hand the androgens may act by suppressing pituitary gonadotrophic stimulation of oestrogen production by the ovary. Fortunately the dose of androgen required in the treatment of these disorders of the menstrual cycle is low, and excellent results are usually obtained by giving 10 mg. of methyltestosterone daily by mouth either for the premenstrual fortnight or continuously for two months, with at least a month's interval between successive courses. It is seldom that such treatment leads to undesirable androgenic side-effects such as acne or facial hirsutism. From the point of view of side-effects there is no point therefore in abandoning the well-established therapeutic regime of giving methyltestosterone. It appears, however, that the new and potent oral progestogens are much more effective than progesterone or ethisterone were in restoring the oestrogen–progesterone balance, and it is likely therefore

that nortestosterone compounds such as *norethisterone* ("primolut N") will replace androgens for these conditions.

The mode of action of androgens in arresting the progress of inoperable breast cancer is still not completely understood. Until recently it was considered necessary to administer high doses of androgens to bring about these results. Even methylandrostenediol and methylandrostanolone were apt to produce virilizing side-effects when given in the large doses needed. There are reports, however, that the new nortestosterone preparations do not give rise to masculinizing manifestations but are effective both in halting the malignant process and also in regenerating bone in the osseous metastases which often accompany the carcinomatous process. This may be due to the anabolic rather than the anti-oestrogenic effect of the drug.

Anabolic Therapy

Androgens are the most potent therapeutic agents at present available for laying down protein in the tissues, especially skeletal muscle and the matrix of bone. Men suffering from deficiency of androgen—eunuchoids and castrates—complain as much of muscular weakness as of lack of secondary sex characters and impotence. Androgenic deficiency secondary to pituitary failure due to such pituitary tumours as craniopharyngioma or chromophobe adenoma results in loss of protein and a negative nitrogen balance. Cushing's syndrome, in which protein is extracted from muscle and bone to be converted to glycogen, leads to osteoporosis and muscular atrophy. Senile osteoporosis is due to lack of oestrogen, which stimulates osteoblasts to lay down calcium and phosphorus in the bone, and to lack of androgen, which is responsible for building up the matrix of the bone upon which the calcium and phosphate are deposited.

The anabolic action of androgens and the osteoblastic activity of oestrogens are therefore beneficial in these conditions. Until recently this was provided by giving a combination of methyltestosterone and an oestrogen such as ethinyloestradiol or stilboestrol. The new potent nortestosterone compounds and other anabolic agents are likely to be more effective than methyltestosterone with less risk of producing virilizing side-effects.

Conclusion

Androgens are administered mainly for three purposes: to provide replacement therapy, to counteract the effect of prolonged or excessive oestrogen influence in certain functional menstrual disorders, and to encourage protein anabolism.

For replacement therapy the most long-acting and economical preparation should be selected. Implantation of testosterone pellets is probably the best way of satisfying these criteria, but the inconvenience of implanting the pellets is a great disadvantage. Long-acting testosterone esters which can be injected weekly (testosterone phenylpropionate), fortnightly (testosterone oenanthate), or monthly (sustanon) are therefore likely to take the place of implants for this purpose.

Androgen therapy in gynaecology is still effectively undertaken by giving methyltestosterone in 10-mg. doses daily. The new 19-nortestosterone compounds, which are powerful oral progestogens, are likely to replace methyltestosterone because they are capable of producing a more physiological remedy by restoring the normal oestrogen–progestogen ratio instead of providing an "anti-oestrogen."

The potent anabolic properties of certain of the new 19-nortestosterone and other compounds may prove valuable in the treatment of osteoporosis and cancer of the breast with osseous metastases.

BOYS WHO COMMIT SEXUAL MISDEMEANOURS

BY

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If not the medical profession, at least many members of the public are apt to think that juvenile sexual delinquency is at least as serious as and probably more dangerous than most other forms of misdemeanour. My experience in dealing with a small number of boys responsible for such misconduct has engendered a degree of optimism with regard to the probable outcome if their cases are handled imaginatively.

Doshay (1943) studied 256 juvenile sex offenders who had been treated at the New York City Children's Court clinics between June, 1928, and June, 1934. None of the 108 of them who had no convictions for offences other than sexual had been known to commit a sex offence in later years, whereas of the remaining 148, who had as children committed other offences as well as sexual ones, only eight were known to commit violations of the sexual code in later life, and the 10 sexual offences committed by these eight were of a comparatively mild nature.

Mannheim (1948) found that the number of sexual offences was very small. In medical literature, however, there seems to be a dearth of contributions specifically dealing with juvenile sexual delinquency, and this justifies the writing of the present paper based, as unfortunately it is, on a small number of cases.

I think that sexual misbehaviour arises to quite a large extent from the need for expression of natural feeling among boys whose lack of self-confidence precludes them from asking from girls a reciprocal expression of instinctive urges in a culture the taboos of which block too many of the avenues to expression of these urges both in childhood and in adolescence. The other situation that seems to me to be of special importance is that some young people are unable to exercise the restraint that official society says that they should, and it is possible that some of these children may be less guilty of want of self-control than are the adults who judge them.

Cases of Indecent Assault

A 16-year-old boy in a country district had sexually assaulted a girl not far from his home. In addition to being brought before the juvenile court he was thrashed by his father, but the local policeman told the probation officer that the boy's father had, in his time, behaved similarly, but by ordinary standards his home was not unsatisfactory. The boy was of low average intelligence, and in interview he seemed to be reasonably adjusted to his environment and did not display any psychological abnormality. He had been referred by the magistrates, and I reported to them that I did not think that the punishment he had had at the hands of his father had been misplaced, and that I felt probation would meet his emotional and educative requirements. A year and nine months later the probation officer

reported that matters appeared to be entirely satisfactory. This boy was one of 17 who were brought to the clinic, usually via the juvenile court, because of some form of indecent assault.

A boy of almost 15 years, who was already on probation, having been convicted of wilful damage, indecent telephone messages, and having no front light, had indecently assaulted a boy aged 3. An intelligence test was not possible at the time, but his school report indicated poor progress, and he was assessed as probably coming into the low average group. He was an immature boy, apparently happy enough in his home but unequal to the social contacts of the outside world, and the psychiatrist recommended that he should have a further period of probation and attend the child-guidance clinic. The magistrates sent the boy to an approved school. Four and a half years later he was found guilty of indecent assault on a girl of 7. It is tempting to wonder if, had he been allowed to remain in his home and to have the psychiatric treatment recommended, he would, at the age of 19, have committed this further offence.

A 16-year-old boy admitted that he had several times put his penis between the legs of his 7-year-old stepsister and had emissions. He was a shy, insecure lad, whose intelligence was estimated as being average and who had been unable to make suitable approaches towards girls of his own age; the psychiatric recommendation was that he should come to the child-guidance clinic. The court accepted this recommendation, and at the same time the probation officer arranged that he should have a change from his unhappy home to living with his married sister. Two and a half years later the probation officer gave a report of very satisfactory progress and development in the meantime.

A boy aged 15 was referred by the court following acts of indecent assault on his small half-brother and half-sister. He was an anxious, well-intentioned child, probably of average intelligence, who felt much insecurity and bewilderment about sexual matters. The psychiatrist offered to see the parents, and suggested that if they were co-operative the boy might be given an absolute discharge. The magistrates adjourned the case for three months, asking the probation officer to keep in touch during this time, and at the end of this period, on receiving a satisfactory report from the probation officer, they gave an absolute discharge. Four and a half years later it was ascertained that the patient was still serving in the Army in the regimental band, but no further details were forthcoming.

A solitary 16-year-old boy of apparently average intelligence, the child of a broken marriage, lived with his father, with whom he had a poor relationship. He sexually assaulted his 5-year-old half-sister, and said that he had done so in order to spite his father, who was her father, too. At the suggestion of the clinic the boy was put on probation for two years with the condition that he resided with an uncle and aunt. This was a happy arrangement, and there was no further trouble during the period of probation, but beyond that time it was not possible to obtain further news.

The next boy, who was almost 13 years old, on several occasions displayed undue interest in the sexual organs of a girl cousin, and there were several other signs of maladjustment and insecurity. His behaviour and attitude were already showing improvement when he was first seen at the clinic, and it was not thought necessary to take him for treatment. More than three years afterwards we obtained a satisfactory report on his progress.

A 16-year-old boy, whose parents were divorced, had been interfering sexually with the little girl next door. Probation was suggested by the clinic and ordered by the court. Two and a half years later the probation officer was able to report very favourably.

A 14-year-old boy of good average intelligence was referred to the clinic on account of attempted sexual intercourse with two girls, aged 5 and 6 respectively. His home appeared satisfactory. He was a very insecure, inhibited boy, a poor mixer, and had wet his bed from the age of 8 until he was 13. He was taken at the clinic for treatment, but was allowed to stop after seven attendances because of his unwillingness to come. For some time after this his behaviour occasioned a good deal of concern at home, but almost seven years after the incident he was stated to be "going along fine."

A boy of 16 was referred by the court following an indecent assault on two little girls, whom he and another boy (next case described) had inveigled into an old motor-car which the boy under consideration had bought, though too young to be allowed to drive. He was in a class at school for retarded "C" stream children. His home background was considered to be indifferent. Some years earlier he had had treatment at another child-guidance clinic, and on the present occasion he was unwilling to have treatment. He also was already on probation at the time of the present offence. Treatment at an approved school was recommended, but the magistrates allowed him to remain on probation. A year later he attended an adult psychiatric out-patient department regularly for 11 months, and from an inquiry 4½ years after the offence it seemed that there had been no further trouble.

The other boy involved was also aged 16. He appeared to be of average intelligence and came from a satisfactory home, his mother having remarried after his father's death five years earlier. He appeared to be a fairly normal boy, and was accepted at the clinic for treatment while on probation. A report from the probation officer 4½ years later indicated that his progress had been most gratifying.

A more difficult case was that of a highly intelligent boy aged 15 who was brought to the clinic by his adoptive parents after there had come to light a long series of incidents of sex play with a little girl who was their natural daughter. The earliest years of his life, before his adoption, had been marked by no small degree of rejection, and on better acquaintance he turned out to be a somewhat affectionless character. A long period of active co-operation between the psychiatrist, the adoptive parents, the children's officer, and the boy's headmaster resulted in a degree of stability, and at the time of writing, 20 months after we first saw him, the outlook is promising.

A 9-year-old boy was brought to the clinic because a policeman's daughter had complained that he asked her to pull her pants down. There were one or two other behaviour disorders, such as stealing and temper tantrums. His intelligence was average. He was taken for treatment at the clinic, and it was felt that he had been helped by 18 attendances. Six years afterwards his headmaster reported that he was much given to stealing and lying, that he was on probation, and that he was slick, apparently full of confidence but backward in school work.

A well-set-up intelligent 16-year-old boy was referred because he had been forcibly holding the hand of a girl who travelled to work in the same train. He was also subject to enuresis. He was shy, insecure, and sexually ill-informed, and the psychiatrist suggested that he might be given a conditional discharge, the condition being that he attend the clinic. The boy promised to accept the condition, and was therefore given an absolute discharge. A good report of him was received some five months afterwards, but no reply has been received to a letter written several years later.

A boy of 16, of average intelligence, was referred to the clinic because he had stolen a motor-cycle, but he had been referred 10 months previously to another clinic because of telling lies and of having interfered sexually with a girl aged 6. He had a sense of grievance against his father, and possibly against adults in general. Two and a quarter years after the first referral he was reported as having married, but being still emotionally unstable.

A boy aged 12 was referred for interfering sexually with his sister. He was an unhappy boy who felt unloved, but he did not wish to attend for treatment, and it was not possible to obtain information about his subsequent progress. The misdemeanour was probably little worse than average behaviour in his social group, but the circumstances are in

line with a concept of my own, to the effect that this sort of behaviour tends to be more common among children who are unhappy or whose capacity for good emotional relationships is impaired.

The two remaining boys who committed indecent assaults did so in rather florid manner.

The first was a 15-year-old of average intelligence who, meeting two girls on the road, exposed himself and tried to feel between their legs and then ran away. He was an only child, whose father had deserted the home some years previously. He was shy and insecure, and had difficulty in mixing with others. He had also several convictions for larceny, but had not been to the clinic before. The psychiatrist recommended to the court that he be placed on probation and allowed to come to the clinic, but the magistrates felt unable to accede to this, and they sent him to a probation hostel in another city. Here he met a man, aged 42, who had homosexual relations with him, and for this they were both brought before the Assize Court in that town. The man was committed to prison and the boy placed on probation, so that he came back home and returned to the child-guidance clinic, where he had about 14 interviews. There appeared to be a substantial improvement in his outlook; he gained a little in self-confidence, and two years after the original episode he was reported to be doing comparatively well and maintaining a fairly steady relationship with a girl friend. An interesting feature was that after the boy's treatment was more or less complete the psychologist said to the psychiatrist, "I thought you were wrong (in expecting a good result from out-patient treatment), but I was mistaken."

The last of the group was a clumsy, shy boy of 15, who might have been regarded as dull and backward had not an intelligence test shown him to be well within the average group. He had attended another child-guidance clinic about three years earlier on account of bed-wetting. His father had long suffered from disseminated sclerosis, and this had produced difficulties which may justify us in considering his home to have been inadequate to the boy's needs. What apparently happened was that he was passing along the street in daylight when he saw several girls of around his own age, who were standing on the pavement, and that he quickly put his hands under their frocks to feel their bodies. It was a flagrant offence, and though he invented a story that he suffered from "black-outs" to explain his behaviour, he had in fact no mental abnormalities of this sort. Nevertheless the magistrates accepted the recommendation of the psychiatrist, to the effect that out-patient treatment at the clinic was what the boy needed, and he was put on probation on the understanding that he would attend. In 12 subsequent interviews the various aspects of his life were discussed, without undue emphasis on sexual matters, and nearly two years after the offence there had been no cause for complaint about his behaviour, and he appeared to be adjusting slowly and with difficulty to social conditions generally. In his case, as in those of not a few of the other boys, the support of the probation officer was a valuable influence.

Sexual Intercourse

A 16-year-old boy had been having sexual intercourse with his girl friend, who was only 14. He appeared to be of average intelligence, and revealed no actual abnormality. His behaviour was the result of want of self-control, and he seemed to be ignorant of the legal sanction against intercourse with a girl of this age. He had been brought before the magistrates, and I suggested that probation would afford him a useful measure of support, guidance, and sympathetic discipline. More than a year later the probation officer stated that the boy had done well in the intervening period, adding that his parents set a fair standard, and that, together with the influence of supervision, he was making an adequate response.

The legal position as regards carnal knowledge seems to me an unsatisfactory one. Apparently a boy of 8 who indulged in sex play with a girl of 15 would be guilty of the offence, whereas a man of 21 who seduced a girl of 16 would not.

By coincidence a second boy aged 16 was referred by the same juvenile court on the same day charged with the same offence, and the girl was also 14. He appeared to be a normal boy of average intelligence, and came from a satisfactory home. Probation was recommended, and the court adopted this recommendation with the result that the probation officer was able to give a very favourable report of the boy a year afterwards.

Indecent Exposure

In three cases the delinquency took the form of indecent exposure.

Kanner (1948) says of exhibitionism that where this is done with a view to deriving gratification from the display of a boy's sexual organs it is rare in children and occurs mostly in retarded and post-encephalitic boys. While agreeing that the offence is commoner in men than in boys, I find it difficult to think that it is so rare in boys or that the boys involved are so usually abnormal. In my own series of 87 delinquent boys, 14 had been referred because of sexual offences, and one of the 14 was a case of indecent exposure (Maclay, 1956), and in my present series of 29 boys who committed sexual misdemeanours of one kind or another three had been brought for this particular offence.

A 15-year-old boy had been assessed as dull and backward by a school medical officer, and he gave this impression also to the psychiatrist—the boy raised spontaneously the question of why he bit his fingers and nails and made a noise with his throat; he spoke of his girl friend, "16 she is; a very pretty girl anyway"—but a subsequent Wechsler-Bellevue test and Schonell word-spelling test, performed by a competent psychologist, gave him an I.Q. of 95, though at school his performance was below average in a "C" stream. He was an insecure, anxious, awkward individual, who said that he had admitted previous similar offences in order to get someone to stop him doing it, but his home background seemed satisfactory. He was offered treatment at the child-guidance clinic, but he came only once, and the probation officer, on probation to whom the boy had been placed for two years, agreed that we let matters lie. The following year the boy stole cycles, and was sent to a nautical approved school. Three and a half years after the original offence he was said to be in the Merchant Navy and to be doing extremely well.

The second boy who had exposed himself was 13 years and 9 months old when referred, and just below average in intelligence. He was an insecure boy who nevertheless had a number of recreations and social contacts. His younger sister, an extremely anxious child, had been referred to the clinic previously, and there was some evidence of a rejecting attitude on the part of the mother. This boy was treated in eight interviews. We dealt first with his interests, his difficulties at school, and recent change of school, made, as he said, because he thought the other boys had something to do with his behaviour as they were telling jokes, and his attitude towards girls, which he agreed was one of fondness coloured by shyness. The therapist said something about girls' strong desire for boys, coloured also by shyness and fear. The next two or three interviews dealt further with his interests and with boy and girl attitudes. The therapist encouraged discussion of adult attitudes, mainly those of his parents, and was ready to encourage expression of and ally himself with the boy's criticism of these attitudes. Almost two interviews were devoted to the discussion in some detail of the anatomy and physiology of reproduction. About this time £5 was stolen from a newspaper shop where the boy delivered papers, and the

owner was inclined to accuse him. The therapist had no reason to think that this boy had taken the money, and the matter was afterwards dropped; in the meantime it was probably an important reassurance to the boy to know that the therapist believed in him and was on his side. At his last treatment interview he appeared to be making a good adjustment both in one or two social contacts with girls and in other respects, particularly in his membership of the A.T.C. A month afterwards he visited the clinic again by arrangement, and brought his sister, who had been a patient a year earlier, and he seemed to be continuing on an even keel. One year later a chance meeting with his school-teacher revealed that at shool he was aggressive, was inclined to show off, and had not endeared himself to his fellows.

A practically orientated psychotherapy of this kind conforms to a maxim layed down by Doshay, who says: "While an acquaintance wtih the psychodynamic principles of psychoanalysis on the part of the psychiatrist is helpful for a proper approach in the process of re-orientating the sex delinquent, *orthodox psychoanalytic treatment* of the juvenile sex offender is *not indicated* and *should be avoided*, because of the likelihood of severe and lasting damage to the personality, arising from the long-drawn-out procedure and the inevitable over-emphasis on the original sex offence, which is diametrically opposite to the needs of these juvenile cases."

The third of these boys was an insecure, shy child, aged 15, who was found guilty in the juvenile court of indecent exposure and of interfering sexually with his younger sisters. Probation was recommended, and this course was adopted by the magistrates. Five and a half years afterwards the probation officer was able to confirm that there had been no further sex difficulty, and that the man was serving in the Army. It was interesting that the probation officer was at that time still in contact with the family in respect of a younger member.

Homosexual Practices

Five boys were referred on account of homosexual acts, and two of these had also been addicted to behaviour of the transvestism type. (I am not, of course, including in this paper boys who may have come to notice because of having been themselves homosexually assaulted, but only cases in which the boys themselves had been regarded as the aggressors in such acts.)

One of these boys was brought by his mother at the age of 12 because he wanted to do feminine things such as putting on ladies' clothes and because he and his brother had been playing sexually with each other in a hayfield. He was a timid child of superior intelligence, and a relevant factor in the case was that his father had recently been indulging in some form of homosexual behaviour, as a result of which the marriage was breaking up. The boy was seen only four times at the clinic, but the psychiatrist was in intermittent touch with his mother for much longer, and more than four years after the boy first came the mother was able to report that he had become well adjusted, and, so far as she knew, had had no recurrence of the sex trouble.

The circumstances of referral of the next boy were out of the ordinary. He was a 15-year-old of average intelligence, who got an average score on the matrix scale, came from what appeared to be a fairly sound home—though the psychiatrist regretted that the environment had no religious background—and had been on probation for two stealing offences when a homosexual offence came to light. The magistrates committed him to an approved school, but the Home Office asked for a psychiatric report. The psychiatrist regarded him as a normally sexed boy, and noted that he took girls to the pictures. He had to remain in the approved school for two years, and at the end of that time the headmaster of the school reported to the psychiatrist very favourably on the boy.

A boy aged 14 of average intelligence was referred by his family doctor on account of homosexual practices with another boy, stealing and wearing women's underclothing, and a theft of money from a neighbour. He was emotionally insecure, an only child in whose home environment there were one or two mildly adverse circumstances. It appeared necessary to see this boy only six times, and in a letter written 18 months afterwards his mother expressed great pleasure in his progress.

A boy of 16 was referred because of homosexual practices with two men in a hotel where he was working, and though he was the victim only, his father stated that from an early age he had been regarded as a "cissy" and had used to enjoy dressing up in his sisters' clothing. His I.Q. was only 73, and he was a poor mixer. By superficial standards his family background was satisfactory. After seeing him four times the psychiatrist told the probation officer, under whose supervision he was, that the boy seemed to be reasonably adjusted and that he need not continue attending the clinic. Almost two years later a probation officer who then had another member of the family on probation considered that our boy was doing fairly well, though associating with a girl of "doubtful character."

In my series of cases there is one other which is too recent for any evaluation of the outcome to be possible, but it had features of such interest as, I think, to justify its inclusion.

A boy of 13 was referred by the court, charged with an indecent assault on a small boy. He was seen while on remand, and so dubious was the psychiatrist about his having committed this particular offence that he strongly recommended to the boy's father that he should be legally represented. To this the father refused to accede, and the boy was found guilty and was placed on probation. An unpleasant feature of the case was that the policeman had extracted a confession by wearing the boy down in an interview which went on through the night until 1 o'clock in the morning. The boy's parents complained that he told lies at home, and they suspected him of stealing; but there came to light also the fact of a very unsatisfactory relationship between the parents, and the father appeared to be guilty of the same sort of disloyalty to the home as that with which they taxed the boy. When charged with the offence the boy said that a baker's roundsman, whom he often helped in a voluntary capacity, would say that he was with him at the time, but to this the man would not testify. The boy attended the clinic several times afterwards, and it was then decided that he need come only to the probation officer, who would help him with the handling of his problems. A few weeks later we heard from the probation officer that the roundsman had been charged with sexual offences against the boy, and that he had pleaded guilty to this charge.

Other Offences

The offence committed by the two remaining boys was not, in the strict sense of the term, a sexual one, and I may not be justified in including it. These two boys broke into a church, defaecated in the minister's vestry, and damaged hymn-books, using pages in the manner of toilet paper.

The boy who appeared to be the leader in the incident was aged 11, of average intelligence, the middle child of three, and came from what was by ordinary standards a good home, though it seemed that his parents had never learned to trust him and were given to hedging him in unduly. He seemed to have little moral sense or consideration for other people and a poor capacity to make warm relationships with others. It was decided to offer to treat him, and the court co-operated by placing him on probation. He had 29 sessions at the clinic, with slow

but apparently satisfactory improvement and increased social sense. It may be worth while to say a little about his treatment, because, of all the boys in the series, he appeared the most inhibited in his capacity to make a relationship, and it was not easy to converse with him. In the sand tray he made a jungle scene—wild-looking, realistic hunters, a village, and a captured zebra in a pen. It was possible by asking questions to get from him what were his hobbies, and from this we got on to the fact that he felt that his father might take more interest in his doings than he did. The boy still made no spontaneous comment. He drew a picture of a battle between wild men and soldiers, and the doctor made an interpretation of his own desire to be wild and free, feelings which were countered by super-ego forces and by the actual authority of his parents.

The therapy continued on the basis of the psychiatrist using any clues he could get hold of as a basis for interpretations or suggestions, which the boy was invited to accept or reject, and most of which he appeared to accept. By the thirteenth interview he produced a little spontaneous comment—for example, "I wish father would stop poking his nose everywhere." Sex was discussed in its mental and physical aspects, and the doctor lent the boy a book on this subject. By the 21st interview the boy was talking freely, though about superficial matters, and this was evidence that he was becoming able to form a relationship with the therapist. In the 25th interview he told the therapist that he had joined the Boys' Brigade. In the 28th interview the doctor tried to find out how the boy would feel about stopping treatment soon, and it came out that he liked coming to the clinic if it got him out of an unpopular lesson at school. It was, however, by no means easy to get this comment from him. After the 30th interview no further treatment was considered necessary, and a report on progress some months later was satisfactory.

As this paper was going to press, I was informed that, almost three years after the original offence was committed, this boy was found guilty of several acts of breaking and entering, and was sent to an approved school. This is regrettable, but it is in keeping with the character of his home background, which we were unable to alter at the time when he was coming for treatment. If we were correct in regarding the original offence as having a sexual coloration, these latter are more in the nature of aggressive acts, and there are grounds for hoping that the approved school will prove remedial.

The other boy who was involved in the incident in the church was also 11 years old. His intelligence was a shade below the average, he was an insecure child and not a good mixer, but his relationships within the home appeared to be good, though there was the suggestion that his father's authority was unduly strict. The psychiatrist recommended that the probation officer be given the opportunity to help this boy, and the court adopted this policy. Eighteen months after the event we had a favourable report on the boy from his minister.

Discussion

There may be a darker side to this picture, and Pearce (1952) says: "The most common form of sexual delinquency is corrupting by talk."

"The more serious forms of sexual delinquency, however, are those in which children live in prostitution —occasionally they are boys."

The following table sets out the conclusions formed from this study of, admittedly, a rather small number of cases.

It is surprising to find in the series so few children of below-average intelligence. Burt (1944), for instance, refers to sexual delinquency in mentally deficient and dull children, but so far as my experience goes, dullness has not been a major contributing factor among boys. Poor emotional adjustment (insecure personality) is the feature that stands out. It would seem also that boys who indulge in sexual delinquencies come, in larger proportion than do boys generally, from homes that fail to give them an adequate measure of emotional support.

Home circumstances	Satisfactory	16
	Less than satisfactory	13
Intelligence*	Below average	4
	Average	23
	Above average	2
Personality	Well adjusted	6
	Insecure	23
Child's subsequent development apparently	Satisfactory	21
	Not satisfactory	3
	In doubt	5

* These assessments are subject to a limitation, in that in a small number of cases there was no opportunity to perform an actual test and the assessment was based on an estimate of the boy's capacity.

It seems clear to anyone who talks to these boys and studies their circumstances that understanding therapy is what they need, and this is likely to provide a better basis for future self-discipline than would stern measures. H. Haas, in a personal communication, has, from his wide experience as a psycho-analyst, told me that he knows of many cases of young people who had gravely transgressed the sexual moral code subscribed to by their elders without these delinquencies coming to light, but who have developed into good citizens of well-adjusted behaviour in adult life. These instances were not confined to his patients, but many were relatives or friends of patients.

The severity with which sexual behaviour among children is often regarded by members of the adult population is due to the internal guilt and anxiety, much of it unconscious, that most members of the adult community bear within themselves; and it is related, therefore, in no small measure to their own rather than their children's sexual conflicts. It is largely for this same reason that adults, whether parents or educators, have so often felt inadequate to giving to children the help they need in handling their problems. Nevertheless there are, allied in this field to-day, many enlightened family doctors, juvenile magistrates, probation officers, leaders in the youth service, marriage counsellors, and parents, and it is becoming increasingly common for dispassionate and understanding attitudes to prevail when sexual misdemeanours come to notice.

Summary

The cases of 29 boys who committed some form of sexual misdemeanour are considered in relation to their home circumstances, intelligence, and personality. From this small study it appears that poor emotional adjustment (insecure personality) and homes that fail to give the children an adequate measure of emotional support are factors that have a positive correlation with the tendency to commit such misdeeds. In the great majority the boy's subsequent sexual development appears to have been good, and support is claimed for a dispassionate and optimistically expectant educative attitude in dealing with this subject.

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PSYCHOGENIC DISORDERS IN CHILDREN

AN EXPERIMENT IN MANAGEMENT

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The Problem

We start with two impressions which we believe will be confirmed by many general practitioners and paediatricians. First, that the proportion of children referred to hospital but found not to have organic disease is high and is increasing; and, second, that there is sometimes a bias against referring children to psychiatric clinics.

What, then, is to be done if, as at a recent paediatric clinic, among eight new cases five were "little belly-achers" with no organic disease to account for their abdominal pains? Or if, as a colleague innocently remarked, among seven new cases at one clinic "there were four enuretics running"? Should they just be sent away? This may be done, after negative physical examination and investigation, with the statement that "there is nothing wrong" or that the child "will grow out of it"—the first always, and the second often, untrue. Or should they be treated by the paediatrician, who, from the psychiatric aspect, is untrained or self-trained? Or should they be referred, sometimes against the inclination of parents or doctors, to a psychiatrist? To assume that each case can promptly be disposed of on its merits is to assume also that these cases can be accurately assessed at an early stage, an assumption which experience shows is often incorrect.

To use a modern analogy: the traffic, already too dense for old roads, is increasing; traffic jams are worsening and bottlenecks are more obvious. To meet such difficulties a by-pass was opened two years ago. As an experiment, we have been trying to deal with some psychogenic disorders by direct co-operation between paediatrician and psychiatric social worker (P.S.W.), with reference to a psychiatrist only in exceptional instances.

One P.S.W. was invited to take a direct part in the work of a paediatric clinic in a general hospital, and another in a clinic at a teaching (children's) hospital.

The Paediatrician's Part

Children with complaints of various sorts, most of them with bodily symptoms such as recurrent pain, enuresis, tics, or tiredness, but some with frankly emotional disturbances, are referred to these clinics by general practitioners in the customary way. A preliminary task is to separate the sheep from the goats, the ovine organic from the caprine emotional disorders—though this statement is a simplification of a complex subject. It is with the non-organic cases that this report is concerned.

In these cases the paediatrician explains in simple terms to the parents, and to older children, how bodily as well as obviously "nervous" symptoms can be associated with emotional stress. The mother is given to understand that the symptom in her child is part of a wider disturbance for which primary organic causes have been carefully ruled out. What does the mother herself think may be the cause? What sort of person does she consider her child is? And what does she feel about the possibility of an associated or underlying nervous disturbance?

When the paediatrician considers that more than simple explanation and reassurance is necessary he may enlist the help of the P.S.W. We find that parents are nearly always willing to co-operate. Possibly because they themselves have experienced such disturbances as headache with worry, "butterflies in the stomach," or diarrhoea before examinations, as a rule they are able to accept the suggested connexion between emotional tension and bodily symptoms.

Another appointment is made for the paediatrician to see the child and parent at a later date, so emphasizing his continued interest and responsibility. Subsequent appointments with him are generally more widely spaced than with the P.S.W.; but he remains readily accessible, affording continued support both to the family and to the P.S.W.

The child and the parent are introduced to the P.S.W. by the paediatrician himself whenever possible, with some preliminary explanation of her functions. In this way the family accepts the P.S.W. as another member of the hospital group concerned in diagnosis and treatment.

The P.S.W.'s Part

The introduction to the P.S.W. is effected in the paediatrician's consulting-room or in the P.S.W.'s own room, which is near by. At the first meeting with the family she tries to make friendly contact, and discusses her part in diagnosis and treatment. According to circumstances she makes further appointments, either at the hospital or in the home, sometimes with the parent alone and sometimes with the child. Subsequently she and the paediatrician discuss the case together and make decisions about management and possible reference elsewhere.

The techniques employed by the P.S.W. are not discussed here. To summarize them would be misleading, and they will form the subject of a further report.

Results

From the therapeutic point of view our cases have been placed in three groups. In the first, the reaction pattern is so set that the situation seems unalterable. In the second, parent or child needs specialized treatment in his or her own right. In the third, which is much the largest group, it is considered that we can help the child to adapt, often with guidance to parents or school-teachers in modifying stresses.

We give figures to illustrate our results, realizing that the material is selected, that methods of selection are not defined or constant, and that there are differences between different clinics.

In two years we have dealt with more than 150 cases by the methods outlined. In about two-thirds the result was satisfactory; symptoms were abolished or relieved, often very promptly but sometimes over a long period,

and the general attitude of the patient (and often of the parents) was improved. One case in five was referred to a child-guidance clinic, usually because treatment by a psychiatrist was necessary, but occasionally for the convenience of the family. In one-tenth of the cases the parents discontinued treatment.

Advantages and Disadvantages of the Method

We set out some obvious or potential disadvantages and advantages, with brief comments.

Disadvantages.—(1) Are serious cases, needing skilled psychiatric care, mishandled or dangerously delayed? We have not found it so. In the event, the approach through a paediatric clinic in which an experienced P.S.W. works often leads to earlier rather than later treatment. (2) Is the participation of a paediatrician a disadvantage? Not, we think, if he is interested in the problems, realizes his limitations, is willing to go on learning, and is fortunate to work with P.S.W.s with whom integration is satisfactory. (3) Can informal, rather superficial, psychotherapy create or bring to light new problems? Occasionally, yes: but these are promptly recognized, and management and disposal adjusted accordingly. (4) Is our method an economic way of deploying P.S.W.s, who are in such short supply? On the whole we think so, as our list of advantages indicates.

Advantages.—(1) The method appeals to parents, patients, and family doctors, with few exceptions. Many of our patients would never reach a psychiatrist, and would remain untreated. The lay public in our districts clearly prefer a medical to a psychiatric centre; this preference may in part reflect the attitude of family doctors. (2) The children attending are, as a rule, much younger than those sent by family and school doctors direct to psychiatrists, and in many the disturbance is milder. The response to treatment is accordingly likely to be better. (3) Psychiatrists, already overburdened, can devote themselves to obviously serious cases in which their skill and experience are essential and irreplaceable. (4) When cases are later referred to a psychiatrist the P.S.W., who already knows the family, may act as a go-between, with obvious advantage. (5) P.S.W.s, paediatricians, and junior medical staff are constantly learning from each other. (We suggest that family doctors benefit indirectly in the same way.) (6) A comprehensive service is provided which in most cases avoids the necessity for transferring patients from one consultant or department to another.

Conclusions

In paediatric practice the tide of physical disorders (due to infection and malnutrition, for example) is receding, and psychogenic disorders are becoming more prominent. Doctors and their associates must adapt to meet changing circumstances. One way might be greatly to augment the number of psychiatrists. We prefer, for many reasons, to expand the interests and scope of paediatricians (and, incidentally, of general practitioners).

Our experiences represent an attempt to improve the services given in paediatric clinics for the common minor emotional disorders of children. The experiment is tentative and preliminary. We have welcomed suggestions and criticisms among ourselves, and also from our colleagues. This preliminary report is published in the hope of evoking them from a wider field, and of comparing methods with others who are attempting to meet the changing circumstances of modern medical practice.

In disorders which are not primarily physical one hesitates to speak of "cures"; but we have been impressed in many cases by the improvement, often quick and dramatic, not only of a symptom but also in the patient's attitude to difficult situations which previously would have provoked a reaction. We do not know what the long-term results will be, but the short-term results seem encouraging. We have no means of comparing our "cure" rate with the spontaneous cure of untreated cases, but most patients serve as their own controls: the improvement with treatment occurs in too many instances, and often too promptly, to be merely coincidental. It is indisputable that most children referred to paediatric clinics with psychosomatic or emotional disorders can be improved with appropriate treatment, without having to be referred to psychiatric clinics.

In this experiment we have been most impressed by the opportunity of dealing with younger, and usually less severely affected, children than those customarily attending psychiatric clinics. This semi-preventive treatment, with interesting new lines of progress which may stem from it, must be important if we believe that "as the twig is bent so the tree will grow."

Nova et Vetera

CHEHOV THE PHYSICIAN
BORN JANUARY 17, 1860

Anton Chehov was born on January 17, 1860, at the small town of Taganrog on the Azov Sea in the south-eastern corner of European Russia. He was the third son of Paviel Chehov, a shopkeeper, and the grandson of Yegor Chehov, a freed serf and bailiff on the estate of his former master, Chertkov. From this grandfather, a man of exceptional will-power and perseverance, Anton may have inherited some of the qualities which characterized him in later years. He himself used to say: "We the children inherit our souls from mother and our gifts from father." His father was a domestic tyrant, and Anton preserved some bitter memories of the whippings he received from him when quite small, and of the brutal way in which the father reprimanded the mother for such minor matters as not putting enough salt in the soup.

Anton's early years were bleak and strenuous. Paviel Chehov had two absorbing hobbies: icon painting and church music. Anton and his two brothers had to rise before dawn on cold winter mornings and were marched off to sing in the church choir. Many years afterwards Chehov wrote of this experience that they "felt like small convicts doing a term of hard labour." Nor was this all that was expected of them. The father's artistic interests made him neglect his shop; money was scarce, and the boys had to take turns behind the counter. The evenings spent at the shop instead of doing his homework were no doubt responsible for Anton becoming backward in his school studies and having to spend a second year in the same class twice running. At the age of 14, while still at school, he was for a time taught tailoring in the evenings, but this scheme was not pursued.

These additional labours, combined with the custom of keeping long religious fasts, must have played their part in undermining Anton's health and reducing his resistance to the disease which subsequently killed him. He fell seriously ill (with peritonitis, probably tuberculous) at the age of 15,

and was devotedly nursed through this illness by the school doctor, whom he always remembered afterwards with admiration and gratitude. When he was 16 Anton's father went bankrupt, and the family moved secretly to Moscow, where the two elder sons were already living, one a journalist, the other a student at the arts school. Anton was left alone at Taganrog to complete his schooling. He succeeded in keeping himself by coaching younger boys in school subjects.

In 1879 he joined his family in Moscow and entered the faculty of medicine at the Moscow University. In later years, when questioned on the reasons why he chose medicine as a career, Chehov used to say that at the time he "had only the vaguest notion about university faculties" and "did not remember what sort of considerations made him choose medicine." He added, however, that he "had never regretted the choice." He may have been influenced, without being clearly aware of it, by the example of the school doctor he had admired as an adolescent. Later, when writing began to claim more and more of his time, Chehov used to refer to medicine as his "legal spouse" and to literature as his "mistress." "When I get tired of one," he wrote, "I go and sleep with the other."

As his father earned a most inadequate wage as a watchman at a Moscow stores, Anton had virtually to keep his mother and his three younger siblings. This he did by writing sketches for a humorous periodical called *The Splinters*. Literary work and medical studies pursued at the same time were a great strain on him, and his letters to the editor often dwell on fatigue, ill-health, and anxiety concerning the approaching examinations. He managed, however, to qualify in 1884, and was immediately offered a minor post by the county council of Zvenigorod, some 40 miles from Moscow, but declined the offer. He started practising in his own neighbourhood at Moscow, for in Russia of those days the custom of selling and buying medical practices did not exist, and any qualified physician could, if he wished, take the risk of opening a surgery wherever he liked. In subsequent years, however, Chehov treated peasants living in the vicinity of his estate, and worked hard during the epidemics of cholera and typhoid fever. In one of his letters of 1887 he mentions having attended a thousand patients during the previous year.

Doctors in Chehov's Plays

It is fascinating to speculate on to what extent Chehov's own experiences as a physician found expression in his literary work. His profession certainly provided him with a very wide field of observation, and he liked portraying doctors in his plays. A doctor character appears in four of his five full-length plays, and several more in his stories. One may hear, perhaps, an echo of Chehov's own ideas on honour and duty in the perorations of the priggish young doctor Lvov in the play *Ivanov*, for as a schoolboy in Taganrog in 1879 Anton was giving advice to his younger brother Mikhail on how a self-respecting youth should behave, while as a young man of 26 he preached to his elder brother Nikolai on the virtues of self-discipline and hard work. Yet he certainly lacked the harsh intolerance and jealous temperament which led this doctor in the play to expose and destroy his rival. As a general practitioner employed by the county in later years, Chehov must have despaired of the effects of his efforts at healing amidst "the dirt, stench, and smoke" of peasant cottages, which drove Astrov, the doctor in *Uncle Vania*, to heavy drinking, but, although he admitted to "smoking a lot and drinking sometimes," he had never made a habit of the latter.

Having acquired a small estate not far from Moscow in 1892, Chehov must have had among his patients some of the local gentry, perhaps even characters like Madame Ranyevskaia in *The Cherry Orchard*, or the actress Arcadina in *The Seagull*, and, being a writer, he might have put some of his own thoughts into the mouth of Dr. Dorn, who, in the latter play, gives such sensible advice to the young writer Trepliov. But, having his family to support all the time, Chehov certainly had had no opportunity for self-indulgence in the Dorn manner. As for the besotted old army doctor Chebootykin in *The Three Sisters*, who "had forgotten everything he had ever learned," this portrait may have been inspired by an actual encounter, but one can be certain that, even if he had lived long enough, Chehov could never have deteriorated in a similar way. There was more than a streak of stoicism, almost of puritanism, in his character which prompted him to efforts beyond his strength. From 1884 onwards, on his own admission, he had been "spitting blood almost every spring," yet he confessed that, like so many of us, he "feared to submit to examination by his colleagues, lest they find something seriously wrong" with him, and he comforted himself with the thought that the trouble was located in his throat rather than in the lungs.

Years of Illness

The death of his brother Nikolai of tuberculosis in 1889 could have been a warning to Anton, yet it did not put him off from undertaking a most strenuous journey to Sahalin, a place of penal servitude, in order to investigate conditions of life there. He returned with his health seriously impaired, and in 1897, after a bad haemorrhage from the lungs, he had to enter a Moscow clinic for investigation. Both lungs were found to be affected, and Chehov was told to change his way of life. "But how can I?" he wrote to his friend, Soovorin. From that time onwards, however, he lived mostly on his estate near Moscow, and later in the Crimea. He was a very sick man when he married in 1901, and his wife, the actress Olga Knipper, had the heart-rending task of looking after him in the last stages of his illness at Badenweiler, in Germany, where he died on the night of July 1–2, 1904.

[Photo by S.C.R.

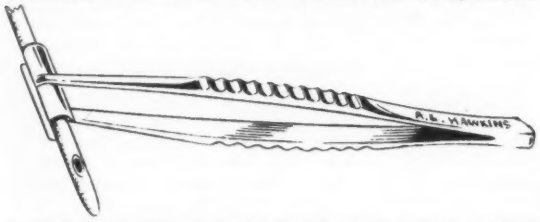
Until his last moments Chehov preserved his sense of humour and his capacity for detachment: on the eve of his death he made his wife laugh at the amusing tales he spun out for her as she sat by his bedside. His few last remarks were to the German physician who attended him and gave him champagne: "It's a long time since I last had champagne," and, "You don't put ice on an empty heart." After a life of very hard work and much suffering his death was easy, and his last thoughts, as always, were for others rather than for himself.

ELISAVETA FEN.

New Appliances

CATHETER-HOLDER

Mr. D. F. ELLISON NASH, surgeon, St. Bartholomew's Hospital, London, writes: Aseptic technique in catheterization is very rarely perfect. Particularly with female patients, the catheter is very easily contaminated during catheterization. It is much safer for the person performing the manœuvre to use a "no touch" technique, and the little catheter-holder illustrated, with one flat and one channelled blade, enables

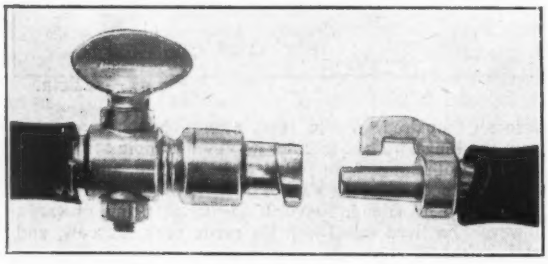


any size of catheter, rubber or plastic, to be inserted without using the fingers. The length of the blade is adequate to maintain rigidity even with soft catheters. It might be said that with rigid catheters no such holder is necessary, but it is only with the large size that insertion can be made by holding the end of the catheter in one's fingers. The insertion of a full-length plastic catheter into the female urethra without touching the labia is quite impossible unless the catheter is held near its tip.

The appliance has been manufactured by A. L. Hawkins & Co., Ltd., 15, New Cavendish Street, London, W.1, and is simple enough to be available in quantity for ward use. It can also be used for holding small cystoscopes and other instruments.

NEW DEVICE FOR SUCTION TUBES

Mr. F. T. CROSSLING, senior surgical registrar, Stobhill Hospital, Glasgow, writes: For some time I have sought a satisfactory means of achieving sterile control of the force of theatre suction. The objects were to reduce the unnecessary attraction of any potential pathogens in the theatre atmosphere which might occur if the sucker was allowed to function throughout a case, and to be able to control the force of the suction so as to obtain satisfactory mucus specimens during bronchoscopy with a distal



collecting apparatus.[1] Also, as a member of the Noise Abatement Society, I am very averse to all unnecessary noise, particularly while operating.

Both the Millin and the Simpson-Smith suction tubes do have a thumb-action on/off control, but they have the disadvantage of being relatively bulky and less manœuvrable in fields other than in the pelvis. The dislodgment of any blood clot is not easy, and these suckers, of course, allow no means of graduating the force of suction. Moreover, with the Millin instrument the distal part can only too easily slip out.

Complete interruption of suction was obtained as often as not by simply applying the handles of a strong pair of forceps across the tubing; but this was not satisfactory—

(*Continued at foot of next column*)

(*Continued from preceding column*)

the manœuvre was clumsy, particularly when being released, and it had a deleterious effect on both forceps and tubing.

The device illustrated has been constructed and found to satisfy all the points described. It is a simple two-piece "gas-tap" with bayonet screw joint to allow for rapid dismantling in the event of blockage and secure reassembly. It is thus extremely easy to clear any blood-clot by simply passing a probe through. The internal diameter is nowhere less than 3.25 mm., which is a shade larger than the smallest diameter of the Wheeler or Poole suction tube. It is best incorporated in the suction tubing about 10–14 cm. proximal to the suction tube for abdominal or thoracic cases. For bronchoscopies it is better to be sited more proximally for regulation by the sister.

I am grateful to Mr. Bury and Mr. Lockhart, of Charles F. Thackray Ltd., for their help in devising this instrument.

[1] Mullard, K. S. (1958). *Brit. med. J.*, **2**, 855.

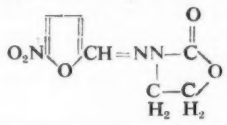
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Furazolidone

"Furoxone" (Smith, Kline, and French).

Chemistry.—This is 3-(5-nitrofurfurylidene-amino)-oxazolidin-2-one, a member of the nitrofuran group of compounds. Its structural formula is as follows:



Pharmacology.—Furazolidone possesses high *in vitro* activity against a wide variety of bacteria, including intestinal pathogens of the genera *Salmonella* and *Shigella*, and concentrations little greater than the minimum required to inhibit growth are also bactericidal.

When administered by the mouth it is partly absorbed and excreted in the urine, and partly retained in the bowel and excreted in the faeces. Much of the dose given cannot be recovered and is presumably destroyed either in the alimentary tract or in the tissues. In doses larger than those recommended for clinical use it has been shown to exert a systemic effect on *Salm. typhimurium* infection in mice, though the organism is not actually eradicated unless treatment is begun very early.

Therapy.—This drug is marketed for the treatment of infective diarrhoea generally, in which its action may be assumed to be mainly local rather than systemic. Studies of its action have been reported from the U.S.A., Mexico, Great Britain, and recently from India.[1] These reports include bacteriological data showing that all or at least some of the patients were infected with recognized intestinal pathogens, and they agree in concluding that the administration of furazolidone in doses equivalent to about 10 mg./kg. body weight daily—e.g., 100 mg. 4 times a day for an adult—is followed by restoration of normal bowel action usually within 3–4 days in the great majority of patients. It is not so clear how often the organism is eliminated; to determine this would require a closer follow-up than appears to have been carried out.

It is not possible on present information to compare the merits of this treatment with those of treatment with antibiotics. One advantage of synthetic antibacterials is that acquired bacterial resistance is less of a problem.

Side-effects.—These have been few, and of a nature (nausea, anorexia) not certainly attributable to the drug.

N.H.S. Basic Price.—100 tabs., 38s. 3d.; 8 fl. oz. suspension, 10s. 4d.

REFERENCE

[1] Massa, A., *Brit. med. J.*, 1959, **2**, 1063.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Chronic Disablement from Neurological Disorders

SIR,—In orthopaedics we are greatly interested in the problem raised by your annotation on this subject (*Journal*, January 2, p. 45). It is, however, a bigger matter than is there suggested.

Although in orthopaedics we have a number of these severely disabled people in the field of poliomyelitis and cerebral palsy, nevertheless there are the cases of congenital crippling deformities and quite a number of young arthritic cripples. No such discussion as has been aroused by Miss A. Whitaker and Dr. M. E. Fearnley would be complete without due recognition of what is already being done in the orthopaedic services of the country: but more could be done. One of the most important, because very practical, observations in the annotation is the idea of "intermittent hospital care with periods at home." The hospital, however, needs to be of special type with all the interests that you mention, and above all a happy creative atmosphere. Our existing country orthopaedic hospitals are just such places. Have people already forgotten Robert Jones, Gauvain, Girdlestone, and many others who pioneered this fundamental idea in social medicine? Orthopaedic hospitals such as those at Oswestry, Nottingham, Edinburgh, Oxford, Alton, Stanmore, Bath, and Exeter have great experience of this work, but I agree that we need some special *homes* for small groups of individuals. Nevertheless, because of the big needs for the ancillary services (social, occupational, and therapeutic), it is desirable that these homes should be in close physical association with such orthopaedic units as I have mentioned, and others like them.—I am, etc.,

Exeter. NORMAN CAPENER.

SIR,—As one who has been concerned for a number of years with chronic disease in the young and geriatric age groups, I was particularly interested in the annotation in your issue of January 2 (p. 45). The procedure of "intermittent hospital care with periods at home" was initiated at Langthorne Hospital four years ago to cater for that category of the elderly called the "aged infirm." It is known as "six weeks in and six weeks out."[1] This has proved a very satisfactory arrangement, especially from the point of view of social therapeutics, and has now become an established feature at Langthorne Hospital.

As the result of experience gained in this field, the technique has been applied to help patients in the younger age groups suffering from chronic neurological disorders. A special ward known as the "Social Rehabilitation Unit" has been equipped and geared to cater for their special needs, and, judging from the heightened morale of patients and relatives, it is clear that a great need has been met. As chronic illness mobilizes aggressiveness, it is important to help the chronic neurological patient to come to terms with his disability and make him one with his family and the community. This is the aim of rehabilitation. Regular periods of six weeks in hospital followed by regular periods of six weeks at home has succeeded in mobilizing patients psychologically, when we have failed to mobilize them physically. The hard line between living at home and living in hospital is blurred with a net gain in favour of living at home. The rhythm of living is altered for both patients and relatives, and their horizons widened. Family affection is thus preserved and a sense of responsibility maintained.

It is the continuity of care which is psychologically crippling, resulting in anxiety-ridden patients, emotionally exhausted relatives, and frustrated general practitioners. As too long a sacrifice can make stone of the heart, alternate hospital and home care has an important role to play in the social problems of chronic disease. Much of this rehabilitation can be accomplished in a domestic setting, and this aspect is worth further study and research.—I am, etc.,

Langthorne Hospital, London, E.11. JOHN DELARGY.

REFERENCE

[1] DeLargy, J., *Lancet*, 1957, **1**, 418.

Breast or Bottle?

SIR,—I find it quite impossible to agree with the statement made on page 72 of the *Medical Research Council Special Report Series* No. 296[1] (and reported in your leading article on December 5, p. 1239) that human milk is an inadequate food for small premature babies in early life. If the whole object of feeding is to obtain a gain in weight more rapid than is normally achieved when the baby remains *in utero*, then I would agree that this can only be done by using a high-protein low-fat cow's milk mixture; but it has yet to be proved that such a thing is beneficial and, indeed, that it will not lead to later complications.

Human milk is the food which is best tolerated by the smallest babies during early life, and it is interesting that all the premature babies in the M.R.C. trials were actually given human milk during the first two weeks of life (see page 33). In our experience premature babies fed on human milk have weight curves comparable to intrauterine growth, provided sufficient calories are given (60 cals./lb. day or 132 cals./kg./day). Both the Swedish[2] and the M.R.C. trials confirm our findings that anaemia and hypoproteinaemia are no more common among babies fed on human milk than among those fed on high-protein cow's milk mixtures. And I agree with the Swedes that the incidence of certain infections is lower among babies fed on human milk than among those fed on cow's milk. I would agree that a high percentage of protein is necessary when cow's milk mixtures are used for premature babies; indeed, we found ample evidence that a diluted full-cream cow's milk mixture with a protein content similar to human milk did not supply sufficient protein to meet the requirements of a premature baby.

It will be a sad thing if the use of human milk for premature babies should be discontinued on such slender evidence as is indicated in Table 35 (page 112) of the M.R.C. report, this Table indicating a smaller mean gain in weight per week among 26 premature babies fed on human milk during the third week of life, 14 babies during the fourth week, 5 babies only during the fifth week, and one solitary baby during the sixth week. With such small numbers it is essential to know whether the babies were male or female, single-born or multiple-born, and their maturities, because all these factors affect the gain in weight, and I could find these particulars nowhere.

It is a pity that such an excellent piece of work as this M.R.C. report should be spoilt by such a startling statement made on so little evidence.—I am, etc.,

Sorrento Maternity Hospital, Birmingham, 13. V. MARY CROSSE.

REFERENCES

[1] Levin, B., Mackay, H. M., Neill, C. A., Oberholzer, V. G., and Whitehead, T. P., *Spec. rep. Ser. med. Res. Coun. (Lond.)*, No. 296, 1959. H.M.S.O., London.
[2] Mellander, O., Vahlquist, B., and Mellbin, T., *Acta paediat. (Uppsala)*, 1959, **48**, Suppl. 116.

SIR,—The disturbing feature of your leading article "Breast or Bottle?" (*Journal*, December 5, 1959, p. 1239) is its title, implying as it does the possibility of doubt. Man is a mammal and likely to remain so, despite his puny meddlings. Medical contraindications to breast-feeding and genuine failure of lactation are common enough without condoning, if not encouraging, deliberate interference with the natural feeding of a normal infant by its normal mother. In fairness to family doctors and midwives it is usually the mother who demands it, and, if the doctor is true to his conscience and protests, she will transfer to another doctor with lower principles.

Artificial foods are excellent, well advertised, and doubtless profitable to their makers. Babies reared on them may very rapidly gain weight, though, as you point out, this is not necessarily desirable. The effects on the mother are more dubious. As an obstetrician and gynaecologist working single-handed in a remote area, I examine personally and repeatedly over the years a large proportion of the women who come under my care. The immediate and long-term benefits to the mother when breast-feeding is recommended and carried through are very evident. The *laissez-faire* attitude of the profession towards the modern fashion to avoid breast-feeding is deplorable. A positive policy of re-education should be jointly pressed forward by public-health workers, family doctors, midwives, and hospital maternity staffs, so that women may return to regarding the breast-feeding of their infants as natural and best. State-subsidized milk for infants should only be made available on a doctor's prescription.

Woman approaching their confinements would be well advised to remember that in these uneasy times the sources and supplies of artificial infant foods may vanish literally in a flash. Radioactive cow's milk from contaminated grasslands may then be the only alternative to breast milk for their suckling infants.—I am, etc.,

Tyrone County Hospital, Omagh. J. H. PATTERSON.

Family Planning Advertisement

SIR,—While your leading article (*Journal*, January 2, p. 42) is somewhat reassuring about Council's willingness and ability to stand up to pressure groups for professional freedom which is traditional in this country, it raises other no less important issues which must be faced.

To have taken almost two weeks to build up and present a case against *The Times* newspaper might indicate commendable inhibition; it does not measure up to the urgency of the situation. *The Times* newspaper is regarded as faultless by its proprietors only. Those who have tried to present an opposing point of view have found that the Freedom of the Press is relative. And, as for accuracy, it must often pass muster where no other facts are presented. Your delay in presenting these facts earlier cannot be laid at their door. Your cry *Tu quoque* is hardly relevant. There is much talk in the Association of the need for a public relations expert. He might well start within the Association by freeing lines of communication between the leadership and the rank and file, who in this unfortunate instance were left at the mercy of newspaper reports and had to believe what it took the leadership so long to deny.

Your last two praagraphs dealing with *mores* is even more serious as an insult to the membership of the Association. Of course all society is concerned with the apparent depreciation in many of the personal and public values. It is indeed necessary that every individual and organized body contribute to the moral welfare of the community. The proposed exclusion of the F.P.A. advertisement is indeed a poor mite to offer as such a contribution by our Association. It is hardly among the readership of the *Family Doctor* that the remedy for society and prophylactic care would seem most urgent.

The main charge against the Council is that in the face of the most extreme problems of medical organization, when general practitioners are doing so little of the medical work for which they so arduously trained, when hospitals are having to cope with the trivialities of both routine general medical needs and industrial cover, when the major problems have been highlighted by numerous committees and reports, when a successful "take-over" of medical organization by private *entrepreneurs* has still further emphasized the lack of constructive planning—our most important professional organization is spending its time splitting hairs in comparison with which the old debates of the number of angels on the head of a pin would seem to have a refreshing charm, even though rather unFreudian.—I am, etc.,

Birmingham, 13. B. BARNETT.

SIR,—Whether or not it was an attempt to emulate *True Confessions*, or copy the periodic public penitences of deviant politicians in certain Democratic Republics, your leading article "O Tempora!" (*Journal*, January 2, p. 42) can be of little satisfaction to members outside the sanctum of B.M.A. House. It may serve a future historian as a time-table of events—as an explanation it is humbug.

Who disclosed the Council agenda in advance to the lay press—Council member, careless secretary, or printer's assistant? Was this a careless blunder or a deliberate attempt to bring external pressure to bear on a private matter? Has suitable disciplinary action been taken against the offender? Until these questions are answered the surmises of the press are essentially those of increasing numbers of doctors who may well wonder whether their virtue and professional reputation might not be better preserved outside the Association. How can you state unequivocally that the Council did not succumb to minority pressure when the matter was not put to the vote?

It is no condemnation of our profession that multiple factions within it will wish to organize themselves into more or less influential pressure groups to formulate and present their particular approach (professional, political, or religious) to medico-social problems, including remuneration. But the Council must soon put the problem to the profession and decide whether or not the primary purpose of the Association is to measure and express majority professional opinion. There are many other organizations of varying character and repute to pursue the interests of convinced minorities. Like the majority of doctors, I am willing

in public to abide by general professional code and opinion, although I may have private reservations. But I fear that the Association is rapidly becoming a public platform for minority dissentients to convince the rest of us we are immoral, anti-social, or uninformed.

It may be we have left reform too late and are already equated, in the eyes of the public, with the authoritative figure so well portrayed by Mr. Peter Sellers in "I'm All Right, Jack."—I am, etc.,

Manchester. GILBERT R. BRACKENRIDGE.

SIR,—The refusal of the B.M.A. to publish the Family Planning Association advertisement in *Getting Married* raises some issues which are independent of the actual content of the advertisement. When, however, you describe it as you do in your leading article (*Journal*, January 2, p. 42) as an advertisement to be 'read, among others, by teen-agers and by the immature" and "which might be held to give the green light to contraceptive practices," it becomes necessary for me to ask you to publish the advertisement itself, in order that your readers may judge for themselves the truth of that statement. The text of the advertisement was as follows:

THE NEWS THAT *MUST* BE WELCOME . . .

When a husband and wife first realise that a new baby is on the way, that should be—*must* be—a moment of supreme happiness for them both.

And it will be—always—in a home where family planning is approached in a logical and sensible manner and where it is understood that to be born in happy carefree circumstances is the birthright of every child.

If you would like to find out more about family planning, why not consult your local Family Planning Clinic—there is one quite near you.

(There follows a list of places where there are F.P.A. clinics.)

For full details of addresses of clinics in your area and times of opening, write to:

Clinic Dept., Family Planning Association,
64, Sloane Street, London, S.W.1.

—I am, etc.,

M. A. PYKE,
Chairman of the Executive Committee,
Family Planning Association.

London, S.W.1.

SIR,—Pending a statement from the Catholic doctors' representatives, which I hope will be forthcoming, I think I am right in saying that no pressure was brought to bear on the Council of the Association to refuse any advertisement in *Family Doctor* by any organized body of Catholic doctors. Indeed, the leading article in the *Journal* of January 2 (p. 42) indicates this quite clearly. Whatever statement was made to a Sunday newspaper by a Catholic surgeon was purely a personal opinion, and not the considered opinion of the body of which he is secretary.

The accusation of religious intolerance, voiced in letters to the *Journal*, is therefore in my opinion quite unjustified.—I am, etc.,

London, S.E.1. W. B. J. PEMBERTON.

SIR,—Your leading article (*Journal*, January 2, p. 42) filled me with amazement. You say, "An advertisement . . . might be held to give the green light to contraceptive practices," especially when read "by teen-agers and by the immature." Does not the Family Planning Association make it quite clear that their advice is only for married couples? And is it not possible that to some people at least the idea that it is possible to plan a family should come from reading "a popular health magazine" and thus lead them to their general practitioner and not the other way round? If you are so concerned with the possible corruption of teen-agers and the immature, why don't you agitate for a reform of our national newspapers, amongst others, from which it may appear that we are a nation of degenerates or perverts? The other day my not yet teen-age daughter, on reading the evening paper, asked, "Daddy, what is soliciting?" What shall I answer to that?—I am, etc.,

Nottingham. G. FIELDING.

SIR,—As a medical officer to several Family Planning Association clinics, and as one who had some experience of general practice, I must condemn the Council's failure to accept the proposed F.P.A. advertisement.

For you to suggest (*Journal*, January 2, p. 42) that one reason for doing so is that such an advertisement might give young people the impression that "the green light [had been given] to contraceptive practices" is just nonsensical. How naive do you think the young people of to-day are? Surely they know that care is taken at our clinics to discourage promiscuity, and, indeed, if it is suspected that our advice will be used to such ends, it will be withheld.

I do think it extremely important that these same young people should know what are the true aims of the Family Planning Association. They are to teach prospective parents how to plan their families so that each child is wanted and so is given the love and care it has a right to expect, and to help couples with their marital difficulties, in so far as we are able. Surely it is far better that young couples should start their married life with such knowledge than perhaps discover it after years of dissatisfaction and maybe unhappiness?

One further point: you seem to fear that the F.P.A. may usurp the function of the general practitioner. In my experience many practitioners are only too glad to refer their patients to us for contraceptive advice. They rightly consider the interests of the patient paramount, and realize that many women feel more at ease with a doctor with whom they have had no previous contact, and one who is, moreover, of the same sex. A lot of women unburden themselves of their problems and fears much more readily to another woman, who usually has a husband and children of her own, than they do to a male practitioner, no matter how respected he may be.

Finally, let us not forget another subject on which many of our clinics now offer advice and investigation—sub-fertility. Surely, even the members of the Roman Catholic Church would approve of this, a subject on which our advice is being increasingly sought to a surprising degree.—I am, etc.,

Darlington,
Co. Durham. JEAN DUBBERLEY.

SIR,—My main objection to most minority "isms" is that they abuse the freedom granted to them by striving to impose their authoritarian doctrines on their more tolerant but comparatively unorganized hosts. Thus we are witnessing the sickening spectacle of an enlightened B.M.A. majority policy being strangled by a small, fanatical, but disproportionately powerful group. The B.M.A. have felt compelled to shelve an F.P.A. advertisement, although its publications have never pretended to represent all the views of all doctors all the time. Certainly the man in the street does not expect

a doctor's public utterances to carry the unanimous approval of his colleagues. Indeed, it is notorious that doctors in public almost always appear at variance even when they stand to suffer for their disunity.

Actually there has been a lot of disagreement about *Family Doctor* publications, and many doctors are known to object to them *in toto*. Little, if any, notice is taken of that until the editors come up against one of these highly organized minorities. Then a majority voice of reason and decency must be suppressed to conform with an authority whose objection is said to be on moral grounds which have already been disposed of by the Archbishop of Canterbury himself. Surely at most the B.M.A. is not called upon to do more than make it clear (if need be) that every advertisement in *Family Doctor* publications is not necessarily personally sponsored by every member of the B.M.A., or even by the editor of *Family Doctor* himself. For instance, the Cremation Society could be permitted to advertise without prejudice to the views of those who prefer to continue to clutter up the earth with their remains.

The purely authoritarian nature of this hold-up is well and truly exposed by Dr. A. D. Clift in his effort to vest it with moral justification in a letter printed on p. 59 of the *Journal* of January 2. Few people in this country would wish to stifle opinion, but let us see how solid are the grounds on which Dr. Clift would show such "genuine concern" as to deprive his patients of *Family Doctor*. He states that the Catholic objection to contraception is based on "natural law." Apparently this "natural law" demands that bodily functions and appetites should not be exercised except for the purely fundamental animal purpose they originally served. The mind boggles at the extent to which any general application of such a "law" would curtail human activities, but even limited to narrow and direct interpretation we should lose the benefit of gluten bread, and perhaps find little solace in reflecting that mothers the world over would finally reject the temptation to shove a dummy teat into their infants' mouths. Of course, neither Dr. Clift nor anyone else recognizes the existence of such a natural law, and it is quite clear that it is postulated to distract attention from the real identity of his authority. Applying it for this purpose, Dr. Clift continues: "In short, contraception is an abuse of the sexual act, as it prevents the primary end of that act—namely, procreation." But unfortunately, even if that conclusion had been derived from sound premises, it is obvious that it does not in fact represent the basis of the Roman Catholic attitude as revealed in practice. For, as Dr. Peter Darby implies on the same page, Roman Catholics propagate "their own inefficient contraceptive methods." Actually some come to place great confidence in their reliability, but it is arrant hypocrisy to suggest that a married couple would deliberately choose the so-called "safe period" for sexual intercourse if their "primary end" was "procreation."

Finally, after exposure of this mass of insincerity Dr. Clift reveals the intolerance that goes with it. He would deprive the right of a majority to the opportunity to come to a reasoned decision in the light of all the facts known about the subject of contraception, and yet would refuse to recognize the claim of anyone who is so genuinely convinced of the virtue of abstinence that he honestly objects to any attempt to push the sale of liquor. Ironically enough, the only valid moral objection to the sale of both liquor and contraceptives is precisely the same. It is held that those who would use them both moderately and well should be sacrificed for the sake of others whose moral fibre is too weak to withstand any temptation to abuse.

However that may be, let us be preserved from "natural laws" and such cant as a basis of anything, let alone as a power to intimidate the B.M.A. even when presented by an "ism."—I am, etc.,

Eye, Suffolk. J. SHACKLETON BAILEY.

SIR,—Is not the British Medical Association a brotherhood of doctors? Has a minority of twenty, twenty-five, thirty per cent. (who knows?) to be driven out by behaviour which it cannot in conscience tolerate? This minority represents twenty centuries of learning and wisdom which will never be deflected by the moods of the moment. Can the Association afford to lose this leavening influence? Can the Association afford to lose two or three thousand seven guineas? If I were a member of Rotary or Round Table I would not expect action or behaviour which would be anathema to me or a minority of members. Indeed, it would not happen.

Your correspondents have quoted freely from *The Times*. I have been an avid reader for twenty years, God forgive me, and I know that you and your correspondents and our long-suffering profession have no reason to be grateful for unwanted advice from the unsympathetic *Times* of London. The Family Planning Association is very well able to take care of its own propaganda and may safely be left to do so without the help of objecting Catholic, and other, doctors.

I am a member of our divisional executive committee and I have great pride and trust in the Association. I am also a member of the Guild of St. Luke, SS. Cosmas and Damian. Now is the time for the Association to close its ranks, preach unity and strength, and face the battles of the coming year, speaking with one voice.—I am, etc.,

Normanton, Yorkshire. A. REEVES.

SIR,—In your leading article "O Tempora!" (*Journal*, January 2, p. 42) you say that at the December meeting of Council the chairman of the Family Doctor Committee asked to withdraw, before a vote, the proposal to accept the advertisement of the Family Planning Association. This request was presumably made because of the opposition of some members of Council. Its effect was to prevent the publication of the advertisement in *Getting Married, 1960*, since the booklet went to press about a week later. Even if Council decides at its meeting later this month to accept the advertisement it will be too late for *Getting Married*, for this year at least.

You say "there are obviously grave doubts about the wisdom of publishing in a popular health magazine issued by the B.M.A. to the public—and read, among others, by teen-agers and by the immature—an advertisement . . ." This argument might apply to *Family Doctor* but hardly to *Getting Married*. One infers from its title that *Getting Married* is aimed at those about to marry or recently married and that its contents are not restricted by the need to avoid disturbing teen-agers. You continue ". . . an advertisement which might be held to give the green light to contraceptive practices." Remembering that we are discussing *Getting Married*, are there still "grave doubts about the wisdom" of acquainting married and engaged couples with the fact that clinics giving birth-control advice exist? This is what the advertisement meant to do and is presumably what you mean by "giving the green light."

You say that no one "can be otherwise than deeply perturbed by the prevailing sexual *mores* . . ." and that this anxiety contributes to the difficulty of deciding whether to publish "an advertisement which might be held to point in a certain direction." The implication of these statements is that the announcement in *Getting Married* that Family Planning Association clinics exist might lead to a lowering of sexual *mores*. This is hard to accept, as F.P.A. clinics see only married and engaged couples.

In your last paragraph you introduce another possible objection to the advertisement, that the general practitioner's position might be affected. Any couple can go to their general practitioner, you point out, and if he wishes he can refer them to the F.P.A. (or National Marriage Guidance Council or other similar body). Does this mean that you do not favour the F.P.A. (or N.M.G.C.) advertising themselves directly to the public ? The question is important, as the majority of patients at F.P.A. clinics are, for various reasons, referred from sources other than their own doctors.—I am, etc.,

London, N.W.7. JOAN M. B. EDWARDS.

SIR,—I have read with considerable relief and amusement your clear and reasonable explanation of the facts pertaining to the decision not to publish an F.P.A. advertisement in *Family Doctor* (*Journal*, January 2, p. 42). The amusement was occasioned by the flatulent celerity with which so many presumably objective people rushed to tilt at yet another giant of Roman Catholic repression—only to find it an innocent windmill, after all.

However, the affair gave me concern on two counts ; first, one would regret the haste with which violent opinions are expressed without the formality of obtaining all the facts and earnestly hope that such a practice is not typical of behaviour in other provinces of experience ; and, second, it would appear from this exhibition of feeling that, although " untrammelled by dogma," many of our professional colleagues are by no means free of prejudice.—I am, etc.,

Bearsden, Dunbartonshire. JOHN A. HAMILTON.

SIR,—I should like to congratulate you on your leading article " O Tempora ! " (*Journal*, January 2, p. 42), provoked by the inaccurate leading articles in which *The Times* attacked the B.M.A. for not accepting an advertisement for its popular health magazine. *The Times*, which had not gained in stature by its recent pretentious advertising campaign, now suffers a further blow to its reputation by the disclosure that it has made serious criticisms of the B.M.A. without ensuring even moderate accuracy as to the facts on which the censure was based. The more " top " a newspaper's readership aspires to be, the less excuse there is for such behaviour. While the anxiety of those who fear minorities within the B.M.A. may be allayed by your leader, it is nevertheless important that mention should be made of another source of pressure—the pressure exerted by commercial organizations with a financial interest in the promotion of contraceptive practices. These commercial interests are not even minority members of the B.M.A., but their financial resources, which are reflected in the scale of their advertising, enable them to exert considerable pressure on medical and lay opinion.

This is, of course, merely one example of a larger and neglected question ; that of regulating the inconvenience caused by the profuse advertising to which our profession is subjected. Is it not time that a determined effort was made to cut down the shoal of literature arriving by every post ? As a first step it could be agreed that envelopes containing advertisements should have the sender's address clearly marked on the envelope (outside) and should when appropriate bear the legend " Unsolicited Advertisement." This arrangement would enable those who do not wish to accept the advertisement to return it at the sender's expense. In time this would lessen the existing nuisance and enable firms to save money at present dissipated in filling wastepaper baskets.—I am, etc.,

Gateshead, 11. JAMES M. FINNERTY.

SIR,—I must congratulate you on your leading article " O Tempora ! " (*Journal*, January 2. p. 42). Thirty years ago the late Dr. Marie Stopes advocated her " scientific birth control " methods with missionary fervour, but at the same time she protested that she did not wish to instruct the unmarried. Fertile marriages and especially the " incorrigibly " fertile were her target. Unmarried persons who applied were, she said, already on the downward path. I believe that the publication of a two-page advertisement from the F.P.A. in any *Getting Married* issue would be of equivalent significance to the " Is Chastity Outmoded? " article which was overwhelmingly condemned in the " Any Answers " programme by the listeners to the B.B.C. While this offending article extolled the pleasures obtained through promiscuity, the advertisement would indicate how maximum pleasure could be obtained by removing the fear of pregnancy. The advertisement would in fact be the logical complement of the article which caused all the hullabaloo.

All local newspapers publish annual reports of the activities of F.P.A. clinics in all parts of the country, and these usually indicate that some unmarried persons apply to them annually for advice. The advertisement proposed by the F.P.A. for *Getting Married* is an obvious extension of this activity. Surely all unmarried persons whatever their age are " getting married " this year, next year, sometime, or hardly ever, and some get married many times, and therefore the F.P.A. in their zeal would like to cater for the lot. One would expect that very small army of practitioners who are engaged as lone hands in instructing private patients in these matters to protest against this take-over bid by the F.P.A. Private practice, it seems, is being encroached upon from every side.—I am, etc.,

Slough. N. C. HYPHER.

Guidance or Treatment

SIR,—While it is quite true, as you said in your leading article (*Journal*, December 19, p. 1391) that before the National Health Service came into being Dr. Blacker recommended that there should be a strict division between " treatment " and " education," and that these recommendations have been repeated from time to time, it should not be forgotten that the last 10 years have enabled several experiments to be undertaken to show how this " iron curtain " could be crossed. In an annotation in the same issue, " Home Help from the Hospital " (*Journal*, December 19, p. 1393), you commend examples of co-operation between the community and hospital services, and I should have thought the combined child-guidance unit was just such an example.

For many years now in the units, provided by the London County Council, as by many other authorities, we have had the psychiatrists appointed and paid by teaching hospitals or hospital boards, the education psychologists by the education officer's department, and working with the school psychological service, and the psychiatric social workers and secretarial staff, as well as the buildings being provided by the public health

department. This has been a most happy mixing and has led to a much better understanding of the problems to be solved, to a removal of suspicion, as great on the educational side as on the medical, and to a dynamic change in the attitude of the community. In a combined unit of this kind the "favouring" of medical or educational views ceases to have meaning, and it is not surprising that this is one of the methods of organization commended by the Ministries of Health and Education.

There is of course a place for the specialized child-psychiatric clinic with beds at its disposal, but this is something other than child guidance, and it is to be hoped that no new barriers will be erected between this and the community service.—I am, etc.,

Public Health Department,
London County Council. DENIS PIRRIE.

Migraine and Hypertension

SIR,—It is a pleasure to read Dr. C. H. Walker's Charles Oliver Hawthorne prize essay (*Journal*, December 26, p. 1430) on migraine and hypertension; it provides a fine example of what can be done in general practice with no more gadgetry than every G.P. carries around with h'm every day.

I should like to make one point arising out of his discussion, which nowhere considers the possibility that migraine itself predisposes to hypertension. I would suggest a possible mechanism in that the vascular spasm which is the preliminary phase of migraine, if it involved the renal arterioles, would set off the vicious circle of renal anoxaemia, leading to hypertension, leading to further renal vascular spasm. This would lead one to wonder whether prevent'on would be possible, perhaps by long-term vasodilator therapy. There seems to be a chance here for a controlled trial, which might interest the College of General Practitioners research unit.—I am, etc.,

Bushey, Herts. D. G. WILSON.

New Drugs for Depression

SIR,—Drs. Peter Dally and William Sargant sound a timely note of warning on the new anti-depressive drugs (*Journal*, December 26, p. 1481). We have recently been conducting a trial of phenelzine, and we feel we should report our findings. Our experience with imipramine has been that it is often advantageous to administer this drug and electroconvulsive therapy concurrently. In this way a more rapid response is sometimes obtained with a minimum of E.C.T. treatments. For this reason we decided to employ the same technique in selected cases, using phenelzine and E.C.T. Of only four patients so treated, two developed alarming reactions a few minutes after apparently normal recovery from E.C.T. These patients collapsed, respiration ceasing in one case, and becoming shallow in the other, and the pulse becoming slow and very weak. Both responded to injections of nikethamide and oxygen under intermittent positive pressure, but the reactions were so severe that we now regard recent phenelzine treatment as an absolute contraindication for E.C.T.

Case 1.—Married woman. 36 years. Strong family history of manic depressive illness. Developed her first manic attack in September, 1959, following childbirth. Was treated with chlorpromazine and E.C.T. Premedication was atropine gr. 1/100 (0.65 mg.) subcutaneously, 30 minutes before treatment. Owing to her extreme resistiveness the first two E.C.T.s were unmodified. Later treatments were modified with thiopentone and suxamethonium. Her tolerance of the E.C.T. was normal throughout; she made an uninterrupted recovery and was discharged seven weeks following admission. She was readmitted in a severe depressive state in mid-November. A course of unmodified E.C.T. was given and again her toleration of the treatment was normal. As her response was regarded as unsatisfactory after five treatments, phenelzine 15 mg. thrice daily was commenced on November 26. She was given E.C.T. on November 28, apparently recovered normally, but a few minutes later respiration ceased and the pulse became imperceptible and a greyish cyanosis was noted. As stated above, she recovered following nikethamide and oxygen under intermittent positive pressure.

Case 2.—A married woman of 49. Admitted on November 10 suffering from a reactive depression with some hysterical features. Was given phenelzine increased rapidly to 45 mg. thrice daily. There was no satisfactory response and the drug was discontinued on December 5. In view of our experience with Case 1, E.C.T. was not commenced until December 11. Premedication was atropine gr. 1/50 (1.3 mg.) subcutaneously, 30 minutes before treatment, and the treatment was modified with thiopentone and suxamethonium. Recovery from treatment was apparently normal, but three or four minutes later respiration became very shallow, and the pulse slow and weak. This patient also responded to nikethamide and oxygen under intermittent positive pressure. Further E.C.T. was given on December 16, and a similar, though milder, delayed reaction was noted.

Phenelzine is said to be very slowly excreted, and our experience suggests that these untoward reactions to E.C.T. can occur as long as 11 days after the drug is discontinued. As one of the cases was modified and the other unmodified, it appears that the reaction is the result of the E.C.T. itself and not due to phenelzine modifying the action of thiopentone or suxamethonium. We should be most interested to know whether any of your readers have experienced similar untoward reactions.—We are, etc.,

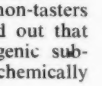
F. A. BLEADEN.
G. CZEKANSKA.

Bracebridge Heath Hospital,
Near Lincoln.

Goitre and Disseminated Sclerosis

SIR,—Various writers have drawn attention to the association of simple goitre in certain cases of disseminated sclerosis, and one of us (A. M. G. C.) has noticed that in more than an expected number of cases there appeared to be a direct association between simple goitre and disseminated sclerosis. The association was sufficiently great to suggest that it should be investigated further, and other writers have drawn attention to both diseases occurring in the same patient. It is difficult to draw any conclusion as to why this is, because simple goitre in certain areas of the country is, of course, very common and probably occurs in about 5–8% of the normal population.

The finding of a goitrogenic compound in certain vegetables such as kale, Brussels sprouts, cabbage, turnips, etc., such as L 5-vinyl-2-thio-oxazolidone ("goitrin") stimulated interest in the production of goitre from the intake of vegetables, and Clements and Wishart[1] felt that the high incidence of goitre in children in Tasmania was due to a goitrogen in milk which had resulted from the cows being fed on kale, and did not occur in milk from cows fed on fodder which did not contain any of the vegetables mentioned.

In this country, Greene, Farran, and Glascock[2] confirmed these findings experimentally on rabbits fed on kale milk. As this goitrogenic compound is related to thiouracil and also to the thiocyanates it was suggested to us that it might have some effect on the nervous system as well as the thyroid. Kitchin, Evans, Clarke, McConnell, and Sheppard[3] recently carried out a survey on the taste response to phenylthiocarbamide (P.T.C.),[4] in which there is a genetic difference in the ability of people to taste this substance. For example, about 30% of white Europeans are non-tasters and 70% tasters. Clarke and co-workers pointed out that this substance was related to the active goitrogenic substances previously mentioned, and all were chemically related, having the same grouping  and they suggested that it would be valuable to test the taste response of various thyroid cases to this substance. In 447 patients with thyroid disease with a control group of 265 using the "eight glass" technique, they found that simple adenomatous goitre had a high incidence of non-tasters which was statistically significant, proportionately greater in men than in women. In 133 patients with toxic goitre a significant excess of tasters was found. Thus it appeared that the result of this test could separate off toxic from non-toxic goitres.

In view of these findings, we have repeated this test on a small series of disseminated sclerotic cases (25). We found that 80% of these cases are tasters and 20% non-tasters, thus demonstrating that the response of cases of disseminated sclerosis is within the normal range and does not appear to run parallel to the findings of Clarke and his co-workers[3] on simple goitre.

Whether the findings of goitre in cases of disseminated sclerosis is purely coincidental cannot be finally stated. In one particular case a sudden exacerbation of the thyroid condition was followed by an acute attack of disseminated sclerosis. It may well be that the same environmental factors which predispose to the development of goitre may also bear some relationship to the occurrence of disseminated sclerosis. It is a point which would bear further investigation, and we still feel that the occurrence of cabbage goitre is worth consideration, particularly in relation to the general metabolic changes. For undoubtedly thiouracil does alter the copper metabolism and cause an increased excretion of copper.

Work is proceeding on these lines. It was felt, however, that it might be valuable to publish our results of a pilot survey on the P.T.C. taste response of cases of disseminated sclerosis, to prevent other people carrying out the same investigation.—We are, etc.,

A. M. G. CAMPBELL.
R. S. CROW.
D. W. LANG.

Bristol, 8.

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[2] Greene, R., Farran, H., and Glascock, R. F., *J. Endocr.*, 1958, **17**, 272.
[3] Kitchin, F. D., Howel-Evans, W., Clarke, C. A., McConnell, R. B., and Sheppard, P. M., *Brit. med. J.*, 1959, **1**, 1069.
[4] Harris, H., and Kalmus, H., *Ann. Eugen. (Lond.)*, 1950, **15**, 24.

"Phisohex"

SIR,—In his letter (*Journal*, December 19, p. 1402) Mr. V. J. Kinsella draws attention to contradictions in the results published by ourselves (*Journal*, October 3, p. 606) and those in the paper by Göpel and his colleagues[1] working at the Robert-Koch Institute in Berlin. Göpel *et al.* use phisohex as a "single shot disinfectant," and we would not dispute that in this respect it appears to be less useful than 80% alcohol. Indeed, Price[2] made this very observation nearly 10 years ago. Since then all workers in the field, with the exception of Göpel *et al.*, have been of the opinion that the excellent initial disinfection by 80% alcohol is quickly overcome by the bacteria-laden sweat within the surgeon's glove during operation. But hands rarely withstand the repeated trauma of scrubbing with highly alkaline soap followed by sharp dehydration in 80% alcohol, which is presumably why this technique is largely ritual. On the other hand, theoretical consideration of the chemical properties of phisohex, both as a non-alkaline soap substitute and as a disinfectant, lead us to hope that it might prove to be a highly efficient detergent disinfectant safe enough to use several times daily for years.

Hexachlorophene, a very powerful bacteriostatic disinfectant, if deposited successfully on skin, will draw a chemical curtain between the reservoirs of bacteria in the deeper layers of the skin and environmental replenishment. If such a barrier could be kept intact it would seem not unreasonable to expect such reservoirs to diminish, perhaps even to disappear. Obviously such an ideal state of affairs would be only rarely achieved, but there is evidence available to suggest that phisohex comes close to accomplishing this. It is at once obvious that such disinfection would take not minutes but several days to become fully established. Most bactericidal disinfectants such as 80% alcohol with their low therapeutic index are unsuitable for such a task, but a powerful bacteriostatic disinfectant with a high therapeutic index such as hexachlorophene could be more useful. This was the concept we set out to test, and we feel that our published results of a trial of phisohex within the arena of its practical application go some way towards a substantiation of such cumulative disinfectant action.

Although Mr. Kinsella suggests that the phisohex film prevents wetting of the bacteria-laden skin by culture media, we would like to reassure him that surgeon's hands when tested were generally soaked with sweat. As finger tips were massaged on to the plate surface free fluid was easily expressed from the media and could be clearly seen alongside and at the base of each streak, mixing sweat with "tween 80." Finally, point 4 of the bacteriological proof in our article clearly demonstrated the value of tween 80 as an inactivator both of hexachlorophene and of phisohex in concentrations far in excess of any to be expected from the surgeon's hands.—We are, etc.,

H. G. SMYLIE.
C. U. WEBSTER.

Department of Bacteriology,
University of Aberdeen.

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[1] Göpel, H., *et al.*, *Chirurg.*, 1958, **29**, 433; 1959, **30**, 116.
[2] Price, P. B., *Ann. Surg.*, 1951, **134**, 476.

Henoch–Schönlein Syndrome

SIR,—We read with interest the memorandum by Dr. C. H. Towner entitled "Familial Incidence of the Henoch–Schönlein Syndrome" (*Journal*, December 19, p. 1385), and take this opportunity of recording two similar cases admitted to this hospital.

Two sisters, A aged 3 years and B aged 6 years, were admitted on March 9, 1959.

Case A.—Admitted with a history of an urticarial rash following penicillin treatment for a tonsillitis. In addition, there had been a history of swelling of face, hands, and feet over a period of one week. On admission she was only mildly ill, and there was a fading macular rash over both legs. There was marked oedema of face, hands, feet, and left knee. Within 24 hours of admission her condition became worse, the oedema becoming more marked and the rash more haemorrhagic. There was a fairly large ecchymosis behind the right knee. She had a loud systolic murmur in mitral and pulmonic areas, conducted radially in all directions. She improved rapidly without relapse. Chest radiograph showed a prominent left ventricle. Since there was no history of cyanosis and femoral pulses were present, the lesion is likely to be a ventricular septal defect.

Case B.—Admitted same day as sister. Nine days before she had developed tonsillitis, and five days later had a scarlatiniform rash. For this she was given penicillin V orally. Shortly afterwards developed an urticarial rash. Two days later the spots had disappeared, but the same evening they reappeared, and ankles, feet, and knees became swollen. On the day of admission the spots became haemorrhagic. Shortly after admission she complained of severe abdominal pain. She had two further relapses in hospital, but when discharged was very well.

	Case A	Case B
Hb	11·6 g./100 ml.	14·0 g./100 ml.
P.C.V.	35	44
M.C.H.C.	33%	32%
W.B.C.	9,600 c.mm.	9,000 c.mm.
Polys	47%	81%
Lymphs	46%	12%
Eosin.	2%	1%
Monos.	4%	5%
Basos.	1%	—
Platelets	372,000 c.mm.	340,000 c.mm.
E.S.R.	22 mm., 1st hour	14 mm., 1st hour
Blood culture	Sterile	Sterile
Faecal occult blood	Positive	Positive
Chest radiograph	? Congenital heart lesion	Negative
Throat swab	*Strep. viridans* and *Neisseria*	*Staph. aureus* (coagulase positive)
Centrifuged urinary deposit	Scanty R.B.C.s	Scanty R.B.C.s
Bleeding-time	5 min.	4 min.
Coagulation-time (Lee and White)	5 min.	6 min.
Hess's test	Negative	Negative
Blood pressure	100/70 mm. Hg	110/70 mm. Hg

We must stress the fact that the diagnosis of anaphylactoid purpura is always a clinical diagnosis, and therefore is sometimes questioned. However, in the two cases described we have no doubts about our diagnoses. Neither mother nor father had a history of any type of allergy or skin trouble.

It is interesting to note that both cases developed tonsillitis about one week before admission, and both cases were treated with phenoxymethylpenicillin. Subsequently in hospital both children were given phenoxymethylpenicillin without recurrence of purpura. The most interesting feature of this report is that it concerns two cases admitted to this hospital within a few hours of each other.

Our thanks are due to Dr. J. Herd Henderson, of Greenock, for referring these cases to us.

—We are, etc.,

Gateside Hospital, Greenock.

ROBERT LAMB.
JEROME P. WALL.

Sensitivity to Phenindione

SIR,—A report of a case of severe diarrhoea due to phenindione appeared in the *Journal* of August 15 (p. 173). As there is apparently no description previous to this I add one of a case which occurred in my own practice.

The patient, a man aged 45, had a myocardial infarction at the end of August, 1959. He was admitted to hospital and given a number of drugs, of which phenindione was one. After an initial loading dose he was maintained on phenindione 75 mg. daily.

Sixteen days after starting therapy he developed loose motions which became progressively more watery. Two stools were examined, and these showed no pus or blood cells and a normal food residue. Culture was negative. The absence of pus from the stools suggested a drug diarrhoea, and the drugs were stopped one by one. Codeine phosphate and mist. kaolin. et morph. were given and a fluid diet taken, but the diarrhoea showed no improvement. Finally the patient was on phenindione alone. The diarrhoea persisted. In view of the degree of angina produced by the effort of repeatedly using the commode the phenindione was stopped. Five days later the stools had returned to normal.

After an interval of a further three days the phenindione was re-started, this time in a dose of 50 mg. daily. Six days later he was having diarrhoea as previously. After another week the phenindione was stopped due to the persistence of diarrhoea. Three days later the stools had returned to normal again.

In view of the need for prolonged anticoagulant therapy—he had a large silent coronary in the United Kingdom in December, 1958, untreated with anticoagulants because of the late diagnosis—the patient is now on ethyl biscoumacetate. Since stopping his phenindione he has had no further diarrhoea. Prior to this the patient's bowel history had been normal.—I am, etc.,

Nairobi. J. H. C. HUNT.

SIR,—The report by Dr. B. E. Juel-Jensen (*Journal*, August 15, p. 173) on a case of sensitivity to phenindione prompts me to report another case where diarrhoea was a side-effect. Unfortunately, at the time, it was not known that the sensitivity would only be bound up with phenindione, and no change to another anticoagulant was contemplated.

The patient, a 50-year-old fruiterer, was seen in August, 1953, for the first time, when he complained of substernal pain, worse on effort, radiating to the shoulders. He also complained of dyspnoea on exertion. An electrocardiograph suggested a left-heart strain with coronary insufficiency. He was digitalized, and glyceryl trinitrate gave him enough relief to carry on with his work. In the course of 1954 his substernal pain became worse, necessitating more frequent doses of glyceryl trinitrate. By June, 1954, the thoracic pain had become so frequent that he was developing a coronary thrombosis. Anticoagulant treatment with dicoumarol was started on June 7, 1954.

On January 8, 1957, "dindevan" (phenindione) was substituted for dicoumarol. On February 26, 1957, he stated that he had been suffering from diarrhoea for three weeks. He was given succinylsulphathiazole without any relief. A bacteriological examination of the faeces and a rectal examination were negative. He was given "thalazole" (phthalylsulphathiazole), "enterocid" (phthalylsulphacetamide), and "entero-vioform" in succession without improvement. A barium enema did not show any pathological lesion.

On July 5, 1957, phenindione was discontinued and the diarrhoea ceased. It recommenced after he resumed taking phenindione. Under these circumstances he was advised to leave off phenindione. He complained of more chest pain than before. In September, 1957, his substernal pain became very frequent. On September 25 he suffered a coronary thrombosis to which he succumbed on the next day.

One can speculate that a change to dicoumarol might have delayed the ultimate outcome, although in

the course of years structural changes of the heart might have precluded any benefit derived from any anticoagulant.—I am, etc.,

Brisbane. E. GUTHANER.

Toxic Cataract

SIR,—I was interested to read the article by Mr. Robert Crawford (*Journal*, December 5, p. 1231) reporting the appearance of toxic cataract in both eyes of a man aged 42 who had been accustomed to take "carbrital" (pentobarbitone and carbromal) for the previous five years.

In his discussion, Mr. Crawford mentions that in the well-known toxic extract induced by 2:4 dinitrophenol less than 1% of those who consumed the drug to combat obesity in the 1930's did actually develop dense irreversible cataracts. He points out that no relation to dosage or duration of use of the drug emerged. We must assume the existence of a considerable degree of individual susceptibility of the lens metabolism to toxic agents, and occasional familial idiosyncrasy has been apparent. Such circumstances may well apply to a patient I have been observing at the ocular motility clinic of the Boston City Hospital.

A 14-year-old girl was treated successfully for esotropia, in which an accommodative element had been elicited, by the use of eyedrops consisting of diisopropyl fluorophosphate 0.025% in peanut oil; a well-known proprietary preparation is used for this purpose in the clinic. After three months, feathery, delicate, silvery-greyish, petaliform patterns appeared, tracing out the architecture of the lens fibres in the anterior subcapsular zones of both eyes. The lens opacities disappeared completely several weeks after stopping the diisopropyl fluorophosphate drops. The lenses have remained clear, but the squint relapsed.

I have avoided use of the term toxic cataract in this case, since the diagnosis was based on slit-lamp microscopy alone and vision was not affected. This case is reported with details and comment elsewhere.[1]—I am, etc.,

RAYMOND HARRISON.

Massachusetts Eye and Ear Infirmary, U.S.A.

REFERENCE

[1] Harrison, R., *Amer. J. Ophthal.*, in press.

SIR,—In Dr. Robert Crawford's article entitled "Toxic Cataract" (*Journal*, December 5, p. 1231) a patient is said to have been described by his doctor as being in perfectly normal health. He is also said to have taken a whole or half capsule of "carbrital" (pentobarbitone and carbromal) every night for five years. Can we be informed how these statements can be reconciled?

If the N.H.S. has supplied a perfectly normal person with from 1,000 to 2,000 capsules of carbrital in five years, it is not surprising that our drug bill is large.—I am, etc.,

Colchester. R. D. REID.

Anaesthetic Vomiting

SIR,—The risks of general anaesthesia are many, but some may be minimized by appropriate precautions. I am therefore anxious to draw attention to a discrepancy between common anaesthetic practice and the known facts about the emptying of the stomach.

The normal emptying time of the stomach is now known to be not *three* hours, as has long been taught, but anything between *five* to *seven* hours. Secondly, this longer time may be even further prolonged by anxiety and other emotional states and by accident trauma. Despite this, it is not uncommon for a general practitioner to refer a patient to a hospital casualty department in the morning, having given the patient permission to take a "light" or an "early" breakfast. Again, much first-aid precept at least condones the popular custom of giving oral stimulants such as tea and brandy after accidents. Such practices cannot be too strongly condemned. In the case of accidents, it follows from what has been said above that it is the "meal-accident" interval and not the "meal-induction" interval that really matters in deciding upon the safety of general anaesthesia.

In conclusion, may I advance the general principle that the taking of liquid or solid by mouth, no matter how little, must be rigidly excluded in any case where the slightest possibility arises of the need for general anaesthesia in the ensuing seven hours? In those emergency cases where this desirable information is unobtainable the hazard has often to be accepted; but, even then, more adequate precautions would, in many cases, be taken if the fact, and the causes, of delayed emptying of the stomach were kept more in mind.—I am, etc.,

General Hospital, Swansea. F. D. ADRIANVALA.

Behind the Depressive Symptom

SIR,—In his criticism of your annotation on this subject, Dr. Robert Thompson (*Journal*, November 28, p. 1179) is, in fact, taking issue with the dogmatism of some of your statements. His use of the term "distress" surely provides the key to the problem to which he refers. This is the universal difficulty experienced at times in distinguishing between so-called reactive and endogenous depressions.

As Curran states,[1] the term reactive has led to confusion because it is applied to both "neurotic" depressions and endogenous depressions *precipitated* by stress (his italics). The latter properly should be regarded as being included in the minority group of cases described by Professor Martin Roth in the syndrome named by him the "calamity syndrome" (see *Journal*, February 28, p. 579).

The problem can be resolved further by the use of the term "primary" to refer to endogenous depressions whatever their aetiological associations. This framework may be a manic-depressive one, involutional, post-influenzal, or a degenerative one from organic cerebral disease. Similarly "secondary" depression will apply to all other cases in which depression occurs as one symptom in an illness which is dominated by an anxiety picture. Thus the causes of secondary depression are as numerous and diverse but, in fact, identical with those responsible for the production of anxiety states. It is to this "secondary" depression that "distress" can correctly and helpfully be applied.

The justification for this nomenclature—*primary depression* on the one hand and *distress* on the other—would seem to be that it *is* possible, although in practice often far from easy, to place cases showing "depression" as a feature in one or other category. This distinction can be made by being alive to the essentially different quality of the symptom in the two groups. In the secondary depression group the distress is a secondary and resultant feature from sustained anxiety. Loss of interest in extra-personal affairs and of capacity for enjoyment, loss of energy, appetite, and sleep, may all be present but are not so sustained and inflexible as in primary depression. They are influenced by environmental changes and are subject to greater spontaneous fluctuations. In particular there is

the familiar difference in pattern of sleep loss which is the most useful single guide in diagnosis. Proneness to suicidal inclinations is not a distinguishing feature in this connexion. Furthermore, neither the absence of retardation nor of an overt alteration in mood are useful in making this distinction. The release of anxiety, agitation, or hysterical features frequently obscures the underlying primary depression, and the powers of compensation of many patients for their true mood depression complete the deception for a time.

The distress associated with sustained anxiety, whether this be occasioned by environmental stress, or by personality difficulty, schizophrenic disorder, or by bodily disease, bears no true relation to the true depression of primary type. The final arbiter in the distinction between primary depression and distress is the response or lack of it to electro-convulsive therapy. This should constitute retrospective proof rather than a diagnostic test. The apparent anomaly of the distress (secondary depression) which responds to this therapy is surely explained by the far from inconceivable coincidence of a minimal level of primary depression being obscured by an anxiety reaction. This may occur as a neurotic response to the primary depression or to any other stress factor and generates distress. By looking beyond the *distress* in such cases the well-defined features of primary depression will, however dimly, be perceived.—I am, etc.,

Carlton Hayes Hospital, Narborough, Leicestershire. JOHN CLEOBURY.

REFERENCE

[1] Curran, D., in *Early Diagnosis*, p. 257, edited by Henry Miller, 1959. E. and S. Livingstone Ltd., Edinburgh and London.

Insulin Syringes

SIR,—In a letter in the *Journal* of April 5, 1958 (p. 827), I suggested that a good deal of confusion could be avoided if soluble insulin of strength 20 units per ml. were abolished, and if insulin syringes were calibrated 40 units per ml. In the tenth edition (1959) of the *Diabetic Manual*, Dr. Elliott P. Joslin writes (p. 169):

"The American Diabetes Association recommends a syringe graduated in units according to whether the insulin is of U-40 or U-80 strength. Our custom has been to use a one cubic centimeter syringe divided into ten parts and then each part would contain 4 to 8 units, depending upon the strength of the insulin, 40 or 80 units to one cubic centimeter. Two strengths of insulin are now on the market—U-40 and U-80 insulin. . . . Some syringes contain 1 cubic centimeter, but instead of being subdivided and designated as tenths of a cubic centimeter are marked in units for the convenience of the patient. Upon one side of the scale the units are given for the use of U-40 insulin; upon the other side of the scale for the stronger U-80 insulin. This avoids the necessity of calculations, but the patient must be careful and read the strength of the insulin printed upon the label on his bottle and then use the corresponding scale of the syringe."

Surely the time has come for us to adopt this rational procedure.—I am, etc.,

Middleton, Lancs. B. HIRSH.

Beyond a Joke?

SIR,—I have read Dr. H. J. Pratap's letter (*Journal*, December 26, 1959, p. 1488) with despondency. The two advertisements (*Journal*, October 17, advertisement page 37; November 14, advertisement page 41) by a shipping line made the best reading for some time in your columns, not because their matter was of medical interest, but because for once (or twice) we were treated to some intelligently contrived and entertainingly presented humour.

I have filed these two advertisements for my own personal amusement when I can reread them. Indeed, I did prepare a reply, in the form of a constructive criticism of the diagnosis and treatment. It was never sent off because I did not know whether it should be sent to you, Sir, or to the advertiser. May your columns be further lightened by more humour, whether from your contributors or from advertisers. Those without a sense of humour do not have to read such matter.—I am, etc.,

Worcester. ANTHONY A. VICKERS.

Boxing Casualties

SIR,—Within recent weeks at least two young men have died from cerebral injuries as a direct result of boxing. In such lamentable cases the coroner's verdict is "Accidental Death." And what of the many permanent disabilities and disfigurements—such as broken noses, cut eyes, impaired cerebration, etc.?

In many, or most, sports there is some risk of injury (accidental), but *only* in boxing is there premeditated intention to cause grievous harm to the opponent. Big Business, no doubt, but insensate, brutal, and sadistic in this year of grace. I suggest that the British Medical Association should use what prestige and influence it has towards the prohibition of boxing, and that, as a first step, no member of the B.M.A. should attend a fight as either a spectator or official doctor.—I am, etc.,

Dundee. F. R. BROWN.

Ghana Medical Service

SIR,—May I wholeheartedly endorse Mr. Harvey Jackson's appreciation (*Journal*, January 2, p. 60) of the Ghana Medical Service, its well-equipped hospitals, and the wealth of clinical material that is to be found in Ghana?

May I point out that the military hospital is the Ghana Military Hospital and not the British? It is partially staffed by seconded members of the Imperial Army Medical Services. I am sure Mr. Harvey Jackson during his visit to this hospital noted the nursing officers of the Ghana Army Nursing Corps, ladies whose devotion to their calling is in the very best tradition of Florence Nightingale and the Army.—I am, etc.,

The War Office, London, S.W.1. W. A. D. DRUMMOND.

POINTS FROM LETTERS

Family Planning Advertisement

Dr. HAMILTON F. MOFFIT (Aberdare, Glam.) writes: I am surprised that you should get so indignant in your leading article "O Tempora!" (*Journal*, January 2, p. 42) over any suggestion that the B.M.A. Council had given in to Roman Catholic pressure and banned the advertisement of the Family Planning Association. Surely it is a well-known fact that for years the B.M.A. Council is most susceptible to the dictates of the Association's Roman Catholic members—ever since the last Dublin A.R.M., when the B.M.A. Council actually hastily withdrew evidence already given on its behalf on divorce—fearing noisy, verbose Roman Catholic protests, as suggested by some resolutions on the A.R.M. agenda.

Obituary

W. R. FEARON, M.B., Sc.D.

Dr. W. R. Fearon, professor of biochemistry in the University of Dublin, died on December 27, 1959. He was 67 years of age.

William Robert Fearon was the only child of a Presbyterian minister, the late Rev. William Fearon, of Kells, Co. Meath. Educated at St. Andrew's College, Dublin, he entered Trinity College in 1911 to read natural science. A year later he began the study of medicine, and then for several years followed both medical and science courses—a feat difficult then, and now impossible. He was awarded the medical scholarship in chemistry, physics, botany, and zoology in 1913, the John Mallet Purser medal for physiology in 1914, the "large gold" medal in the natural science moderatorship (B.A.) in 1915, and a foundation scholarship in experimental science in 1917. In the same year he won the vice-chancellor's prize for English verse, the set subject being "The Retreat from Mons." This was but one of many indications of the astonishing versatility which characterized his whole career.

About this time he interrupted his medical studies to undertake research on nutrition, at first in London and afterwards at Cambridge, where he worked with Gowland Hopkins during the tenure of an exhibition in Emmanuel College. This work gained him the Dublin Sc.D. in 1919, and, returning there, he was appointed assistant to the King's professor of institutes of medicine (physiology). In 1921 he was elected to fellowship of Trinity College and appointed lecturer in biochemistry. He completed the medical course and graduated M.B. in 1929. He continued to act as assistant in physiology until 1934, when the chair of biochemistry was founded expressly for him. In the succeeding years he rarely left Dublin, and even during the vacations he was to be found quietly working in his laboratory almost every day. He was a senior Fellow of Trinity College.

His researches in biochemistry covered a wide field. As he had been a pupil of the late E. A. Werner, it was not surprising that some of his earliest work concerned the formation of urea from protein. The dietary exigencies of the first world war turned his attention to nutrition, and his interest in this pervaded much of his subsequent work. Besides many papers, he published the book *Nutritional Factors in Disease* (1937), and he also did much unobserved and unrewarded work on official and other committees and advisory bodies, particularly during and after the last war. In 1948 he organized a survey of the fluoride content of drinking-water from various parts of Ireland. Always fascinated by colour reactions, he was specially interested in trying to establish microcolour reactions for individual amino-acids. A notable contribution to general biochemistry was his work on the periodic classification of the biological elements (1951). The first edition of his textbook *An Introduction to Biochemistry* appeared in 1934, and he was at work on a fourth edition up to the time of his death. As a teacher he was clear and precise, and his lectures, always carefully prepared, were illuminated by his great breadth of interest and by his sparkling wit. There were no arid patches in his exposition, nor sleeping students in his auditory.

His early interest in other cultures than science remained throughout his life. As a young man he had many friends among the notabilities of Dublin in art and letters—the Yeats brothers, Sarah Purser, Gogarty, and members of the Abbey Theatre Group. In 1937 he wrote a play, *Parnell of Avondale*, which ran successfully in that theatre. A great lover of music, he was an accomplished performer on both pianoforte and organ. His hobbies were his large stamp-collection and motor-cars, old and new.

Always reserved in personal matters, he grew more so in later years, but his sympathy and understanding, particularly for students and their difficulties, never failed. During his lifetime he touched on many aspects of learning and of human interest, and (as was written of another son of Trinity) touched nothing that he did not adorn.

He was unmarried, he had no near relations, and but few close friends. For these, and for his school and its students, the loss is great indeed.—D. T.

G. C. D. writes: It was very sad news to hear of the death of my friend William Fearon. He was the wittiest and cleverest person I have known. I met him first when I mistook him for a more senior medical student, when, in fact, he was a Fellow of Trinity College, Dublin, and professor of biochemistry, and that inauspicious beginning was the start of a 35-years friendship.

His personal appearance was misleading: he had a receding chin and weak, blinking eyes, and it came as a surprise to hear a deep, authoritative, pleasant voice, delivered in a serious tone, but soon enlivened by a shaft of wit. In his introductory lecture to the biochemistry course he mentioned that the word was derived from "bios," meaning life, but for a human being to try to define life was like trying to wheel oneself in a wheelbarrow.

He lived with and looked after his old mother, who died some years ago. His father had died when he was an infant, and his mother had worked hard to bring him up. Only last summer he had pointed to the rather overgrown square, Clarinda Park, Dunlaoghaire, and said, "That is my green elephant." He had bought it some time before so that his mother could walk about in it. He never married. On hearing that the professor of Spanish had married an Italian lady, he remarked that perhaps he, being a biochemist, should look out for a structural formula.

Although Fearon sometimes quoted Disraeli's saying, "I must be failing. I don't seem to be able to retain my enemies in the way I used to do," this remark was singularly inapplicable to himself, and I never remember him speaking harshly, or too unkindly, of anyone.

J. E. A. UNDERWOOD, C.B.E., M.B., B.S., D.P.H.

Dr. J. E. A. Underwood, formerly principal medical officer, Ministry of Education, died suddenly on December 31, 1959, at the age of 73.

John Ernest Alfred Underwood was born on December 25, 1886, and educated at Blackheath School and University College, London, where he graduated B.Sc. in 1910. Going on to study medicine at University College Hospital, he qualified in 1915, and then held resident posts at his teaching hospital before joining the R.A.M.C. for service in France and India during the first world war. After demobilization he graduated M.B., B.S. in 1920, obtaining the D.P.H. a a year later, when he became assistant medical officer of health and assistant school medical officer of Willesden. After four years in Willesden he joined the staff of the Board of Education and succeeded Dr. J. Alison Glover as principal medical officer in 1941. In 1948 he was appointed C.B.E. He retired in 1951.

At an early stage in Dr. Underwood's career with the Board of Education he was given special responsibility for dealing with questions regarding vision and hearing and with the education of partially sighted and partially deaf children. In 1931 he represented the British Government at the international conference in New York on the welfare of the blind; he was secretary of the committee on partially sighted children (1932–4), and vice-chairman of the committee on children with defective hearing (1934–8). In 1950 the Ministry of Education committee on maladjusted children was appointed, and although Dr. Underwood was about to reach retiring age it was felt that he was the best possible choice for the chairmanship. Accordingly he gave devoted service for several years in this capacity, and as a result the committee's report is usually referred to as the Underwood report.

R. W. writes: When I joined the staff of the Board of Education, Underwood was my immediate senior, and it

became one of his responsibilities to help the new recruit in learning the ways of a central government department. For some time I accompanied him on his visits of inspection, and it soon became evident to me that the school medical officers of local authorities looked forward to those visits; they regarded him not as an inspector but as a guide, philosopher, and friend. One of the reasons for this was that he was an exceptionally good listener. I never heard him interrupt anyone during an argument or discussion, and as a result any criticisms and suggestions which he had to make were accepted in the best possible spirit. After he was promoted, and his work tied him to a large extent to the Ministry's headquarters, many of the local authority medical officers whom he had known in earlier days continued to regard him as a personal friend.

Underwood had read widely, and he derived much pleasure from music. Among his other recreational interests golf had a high place, and until the war put an end to it he and I had a standing engagement for a week-end round. Those games have provided, and will continue to provide, happy memories of a colleague whose kindness was never-failing.

Dr. Underwood was married, and to his widow we extend our sincere sympathy.

L. FREEMAN MARKS, M.B.

Dr. L. F. Marks, who practised in Swansea for nearly fifty years, died in hospital on December 22 after a brief illness, aged 88. A senior member of the profession in South Wales, he was elected a Fellow of the B.M.A. last year.

Leonard Freeman Marks was born on September 9, 1871, and studied medicine at University College and St. Bartholomew's Hospital, qualifying in 1896 and graduating M.B. in 1901. Before entering general practice he held appointments at Bart's, and served as house-physician and house-surgeon to the Swansea General and Eye Hospital, the hospital in which he died. In 1900 he went into general practice in Mumbles, Swansea, remaining at work there until just before the introduction of the National Health Service. He took a great interest in first-aid work, serving as medical officer in charge of a local Red Cross hospital during the first world war and as medical officer to a first-aid post during the last war. His work and enthusiasm during the second world war were much appreciated by all who knew him, since it was known that he was carrying on with the grave disadvantage of defective vision. His response to emergency work at night was remarkable, for travelling in the "black-out" must have been to him a nightmare.

Outside his family and religious life the B.M.A. was his great love, and his election last year as a Fellow of the Association was a fitting tribute to his life's work, giving him extreme pleasure. He served the B.M.A.'s interests with zeal and enthusiasm, and in the course of his life was elected to most of the provincial offices that could be held, having been honorary secretary of the Swansea Division in 1908 and several years thereafter, representative of the Division at a number of Annual Meetings, chairman of the Division from 1913 to 1914, and president of the South Wales and Monmouth Branch from 1933 to 1934. For many years he was a member of the Welsh Committee. During the difficult years before and after the passing of the National Health Insurance Act of 1911 he was honorary secretary of the local provisional medical committee.

Leonard Marks was a quiet and reserved man, admired and respected by his colleagues, friends, and patients alike, particularly for his strong beliefs and affection for his home life. From his earliest days until his death he was a staunch member of his church, "The Brethren." He was indeed one of the pillars of his faith in Swansea, and will not easily be replaced. He suffered a great loss during the last war when his first wife died after many happy years of married life, for she had given him great help and encouragement during his professional life. They had four children, one of whom, Colonel R. L. Marks, O.B.E., R.A.M.C., entered medicine and made the Army his career. Some years after the death of his first wife Dr. Marks married again, and to his widow, who gave him most devoted attention, and to his children we extend our sympathy.—F. M. L. J.

CLARICE G. RAHA, M.B.

Dr. Clarice G. Raha died in Calcutta on May 3, 1959, as a result of burns sustained while going to the help of her sister. She was 65 years of age.

Clarice Grace Raha was born in Calcutta and studied medicine in that city, graduating M.B. in 1921. During her career she spent many years in Burma and England, but most of her work was carried out in India, the place nearest and dearest to her heart. Both in Delhi and in Calcutta she did much to encourage maternity and child-welfare work in India, helping to establish ante- and post-natal clinics, nurseries, and V.D. clinics. For many years she was attached to the out-patient department of the Eden Hospital and to the V.D. clinics of the Medical College Hospitals, and she also had a private practice. Her work was truly self-sacrificing, and in her passing the medical profession has lost a worthy colleague.

DAVID DUFF, C.M.G., M.D., D.P.H.

Dr. David Duff, formerly director of medical services, Gold Coast, died on September 27, 1959, at his home in Annascaul, Co. Kerry. He was 76 years of age.

David Duff was born in Enniskillen on April 11, 1883, and was educated at Portora, Enniskillen, and Trinity College, Dublin, to which he won a classical scholarship. He graduated M.B., B.Ch., B.A.O. in 1909. In 1914 he took the D.P.H. R.C.S.I., and in 1918 proceeded M.D., when he gained the Gold Medal. He was called to the bar at Gray's Inn in 1927. He first went to Africa to assist in the research on malaria being carried out by Sir Ronald Ross. Later he joined the West African Medical Staff, Colonial Medical Service, in which he spent most of his working life, finishing as director of medical services in what was then the Gold Coast Colony.

In his early days he served in remote stations, only accessible by narrow tracks, and he acquired a knowledge of the country and its customs and people better than most men. He spoke Fanti and Hausa fluently, and was an examiner in both. He had a great affection for the people of the then Gold Coast. Once in an interview with the late King George VI he said, "Sire, they are a *good* people." Returning to the West Coast of Africa from leave in the United Kingdom early in the first world war on the s.s. *Appam*, he was captured by a German raider which was chased across the Atlantic and eventually delivered its prize into one of the harbours of the U.S.A.—at that time neutral.

He was a great reader and kept up his knowledge of Greek by taking a Greek newspaper from his schooldays onwards. It was a fascination to listen to him arguing over a Greek root. After his retirement in 1939 he learned Erse. During the second world war he served as a medical officer in the Ministry of Health in the West of England, finally retiring in 1946 to the Dingle peninsula, overlooking Castlemaine harbour and the Macgillicuddy Reeks. He was a very accomplished chess player and, for one so gifted, a remarkably modest and unassuming man. He was appointed C.M.G. for his distinguished services in the Gold Coast, now Ghana.

David Duff's passing is deeply regretted by a whole host of friends—African and European—who will always remember him as the most considerate and kindliest of men. He was twice married, the second time to his deceased wife's sister, who mourns his passing.—S. S.-C.

A. L. LEVY, M.B., Ch.B.

Dr. A. L. Levy, senior registrar in clinical pathology to the United Manchester Hospitals, died on October 2, 1959, in the Manchester Royal Infirmary after a major operation. He was 32 years of age.

Abraham Leo Levy was born in Manchester and received his earlier education at Manchester Central High School, where he gained a city scholarship to the University of Manchester. Though a series of unfortunate incidents of ill-health interfered with his career, both before and after he became a medical student, he entered the medical school in 1947 and graduated M.B., Ch.B. in 1953. Thereafter he held resident appointments at the Victoria Memorial Jewish Hospital and Crumpsall Hospital, Manchester, and was senior house officer in medicine at Ashton-under-Lyne.

In 1955 he began his career in pathology at Crumpsall Hospital, where he made steady progress, and was successively resident clinical pathologist, senior house officer, and registrar. He was appointed registrar to the Manchester Royal Infirmary in 1958, and later he became senior registrar. All who came in contact with him were impressed with his ability and knowledge, and it was felt that he was on the threshold of a promising career. His passing came as a great shock to his many friends and medical colleagues, for he gave no indication of the great stress under which he must undoubtedly have worked. His ability to succeed in the face of adversity borne with fortitude was an example to all who knew him. He was a man of sincere religious beliefs, and this would explain his stoical attitude to life.

Dr. JAMES DAVSON writes: I first knew A. L. Levy as one of my resident clinical pathologists, and soon realized that his rather severe handicap of shyness was more than compensated by an intelligent, alert, and well-stored mind. In his work he was a careful, methodical pathologist, and experience convinced me that he could be relied on in each branch of clinical pathology in which he worked. He quickly rose to the level of registrar in pathology, and then, in due course, he obtained a post as senior registrar at Manchester Royal Infirmary, although he had been dogged by ill-health of a mysterious kind almost throughout his career as a clinical pathologist. This he bore with unexampled fortitude and patience, and with a quiet courage that must compel the admiration of the few who knew the formal diagnosis and its implied outcome. Levy was very well liked by his colleagues and in the laboratory and in the hospital, and was a loyal assistant who will be remembered with admiration and affection.

Dr. MICHAEL CASSON writes: Those of us who knew Leo Levy well realized that behind his retiring appearance he was a man of very warm and sympathetic personality. He never complained of his severe infirmities of long standing, his terminal illness coming as a complete surprise to many of his professional colleagues. He was a person of sound judgement and great trustworthiness, both in his work and with his friends. He will be deeply missed by many who had great affection for him.

E. P. CAREY, M.B., B.Ch., B.Sc., LL.D.(Hon.)

Dr. E. P. Carey, who had been in general practice in Lewisham for 35 years, died in the Miller Hospital, Greenwich, on December 10, 1959, at the age of 69.

Edward Patrick Carey was born in Killarney on July 18, 1890, and educated at St. Brendan's Seminary and University College, Dublin, where he graduated M.B., B.Ch. in 1914, having previously obtained both the B.A. and B.Sc. degrees. It was typical of him that, when reading in his morning newspaper during the first world war that there was a shortage of doctors for the Western Front, he promptly resigned his position in the Irish practice in which he was safely and firmly established, and volunteered for the R.A.M.C.

Shortly after the war he set up in practice in Lewisham with his brother, Charles F. Carey. His skill, kindness, and zeal soon endeared him to the people of that district, where for the next 35 years his was a well-known figure. To the patients he was essentially a family doctor who took a deep personal interest in every aspect of their welfare. To his fellow doctors he was a loyal colleague, and as a staunch member of the B.M.A. he regularly attended the meetings at Lewisham Hospital. In due time he became president of the West Kent Medical Society, and, as a Catholic, he was an influential member of the Guild of SS. Luke, Cosmas, and Damian.

His services to his Church were legion, and as honorary medical officer he often accompanied the Southwark Diocesan Pilgrimage to Lourdes, and was unfailing in his attendance on the sick on the long journeys to and from the Pyrenees. For his distinguished services Pope Pius XII conferred upon him the cross *Pro Ecclesia et Pontifice*. Further recognition came in 1955, when he was created a Knight of the Holy Sepulchre of Jerusalem.

"E. P.," as Carey was known, will be remembered especially for his work among his fellow Irishmen in England, and a permanent memorial to his zealous efforts may be seen in the National University of Ireland Club in London, which he helped to found in 1929. From its inception he served upon its council, and held the office of president for two separate periods. He was always most anxious that Irish graduates should play their part in giving leadership to the Irish in Britain. In recognition of this work the senate of the National University of Ireland conferred upon him in 1954 an honorary Doctorate of Laws.

Dr. Carey's interests were wide, ranging from his one-time presidency of the London Irish Medical Golfing Society to his membership of the Irish Literary Society and the Irish Text Society. He also found time to be a vice-president of the Irish Club and an active member of the executive committee of the Irish Centre. He was a keen admirer of Paul Henry and J. H. Craig, both of whose works adorn the walls of his home along with the paintings of his more intimate friend, Jack B. Yeats. He had also numbered among his collection the works of younger men, whose later rise to fame has confirmed his soundness of judgment.

His funeral in Dublin was attended by the President of Ireland, the Chancellor of the University, Mr. Éamon De Valera, by high dignitaries of the Church, by members of the Cabinet of the Irish Republic, and by representatives of many public bodies.

Dr. Carey is survived by his widow and six children, his three sons having followed him into the medical profession. The sympathy of his friends goes to his family and to his partners.—J. L. and M. D. N.

C. H. BRYANT, M.D., F.R.C.S.

The obituary of Mr. C. H. Bryant was published in the *Journal* of January 2 (p. 64).

Sir WILLIAM SAVAGE writes: In those far days of over 60 years ago Bryant and I were both residents at the Sussex County Hospital, he as house-surgeon and I first as pathologist and later as house-physician. He was house-surgeon all the year I lived there, and never, so far as I know, house-physician, as stated in the obituary. There were then only four residents, and we were a united team working admirably together, and much of this was due to Bryant, who was the senior resident. We usually forgathered after dinner in his room, and he used whimsically to point out that, while we each had our own room, *his* room seemed to be common property. He was a brilliant operator and a very skilled surgeon, and I frequently gave the anaesthetic for him. When no visiting surgeon was available he carried out some very difficult operations. I fear his skill militated against an appointment later as a visiting surgeon—which he wanted. He was a man of great charm, and I never saw him ruffled: we all admired him very much. Later I saw no more of him, for he went on to a brilliant career, while I migrated from Brighton to my old hospital (U.C.H.) to teach pathology and bacteriology. I have, however, never forgotten him, and offer this little tribute from 87 years of age to his of 88.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 26** (No. 51) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	2	0	2	4	1	6	0	1
Dysentery ..	683	110	122	5	3	1,210	92	156	14	8
Encephalitis, acute	5	0		0		6	0		0	
Enteric fever:										
Typhoid ..	1	0	0	1		5	1	1	0	
Paratyphoid ..	4	0	0	0	4(B)	2	0	1(B)	0	
Food-poisoning ..	164	10	6	0		168	18	21	0	
Infective enteritis or diarrhoea under 2 years				4	18				16	21
Measles*	948	18	21	3	17	10,113	666	140	40	428
Meningococcal infection	14	2	7	1		19	1	8	0	1
Ophthalmia neonatorum	8	1	3	0		20	3	7	0	
Pneumonia† ..	233	19	200	2		527	32	371	7	
Poliomyelitis, acute:										
Paralytic ..	1	0	0	0	1	18	0	1	0	2
Non-paralytic ..	1	1	0			10	0			
Puerperal fever§ ..	125	13	4	0	1	179	31	23	2	1
Scarlet fever ..	1,001	47	91	9	23	1,283	85	90	25	32
Tuberculosis:										
Respiratory ..	262	38	45	5		479	54	95	17	
Non-respiratory	31	2	8	3		62	8	16	3	
Whooping-cough	371	42	93	3	24	530	27	50	64	58

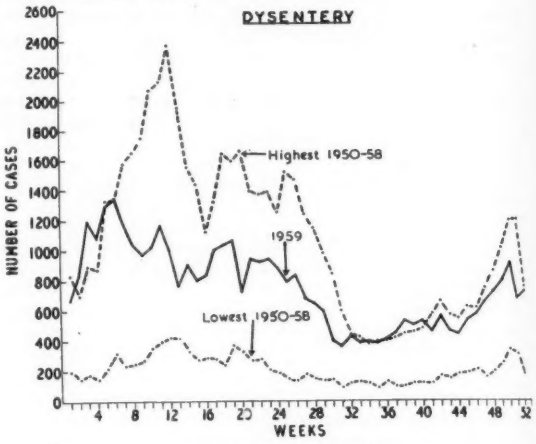
DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0		0	0	0	0	0
Dysentery ..	0	0		0		1	0		0	
Encephalitis, acute		0					0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	13	0	0	0		5	0	1	0	2
Influenza	17	0	0	0		37	3	3	0	1
Measles		0	0	0			0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	480	42	27	9		778	61	27	26	21
Poliomyelitis, acute	2	0		0		4	0		0	0
Scarlet fever ..		0	0	0			0	0	0	0
Tuberculosis:										
Respiratory ..	63	4	6	1		112	7	13	3	1
Non-respiratory		1	0	1			0	2	0	0
Whooping-cough	1	1	2	0		0	0	0	2	0
Deaths 0–1 year ..	270	33	30	4		327	31	32	9	15
Deaths (excluding stillbirths) ..	8,967	652	607	123		12,440	1033	737	170	199
LIVE BIRTHS ..	8,409	775	705	164		13,520	1122	1050	203	306
STILLBIRTHS ..	189	14	20			319	17	23		

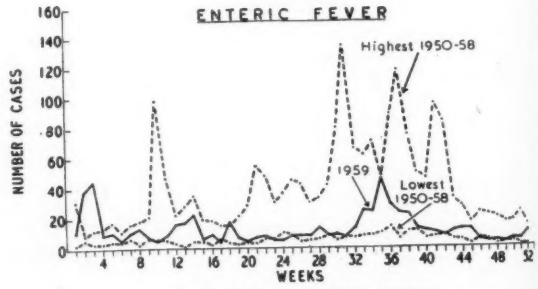
* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

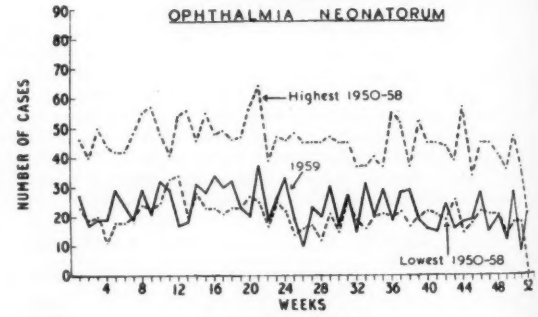
Vital Statistics

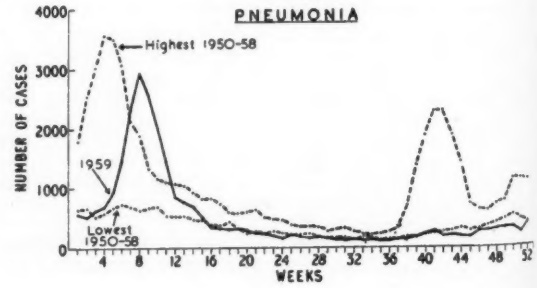
Graphs of Infectious Diseases

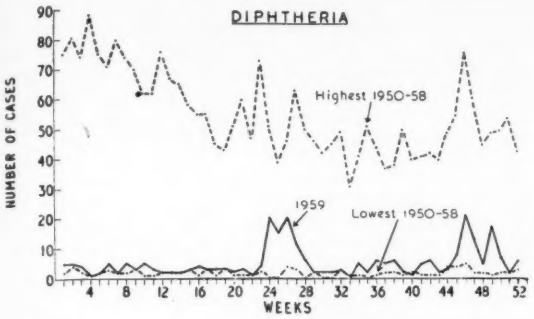
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

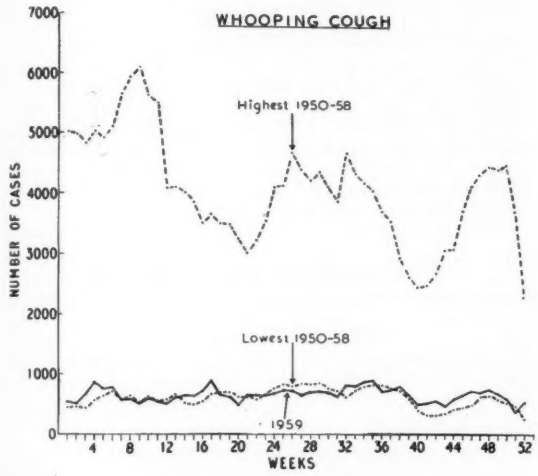


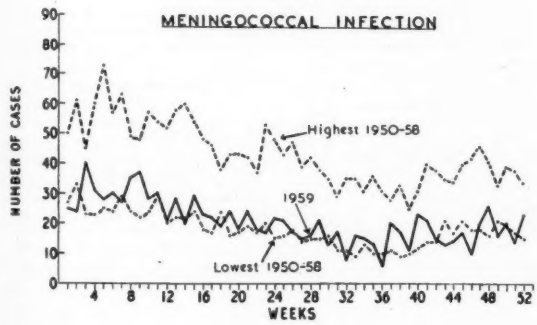


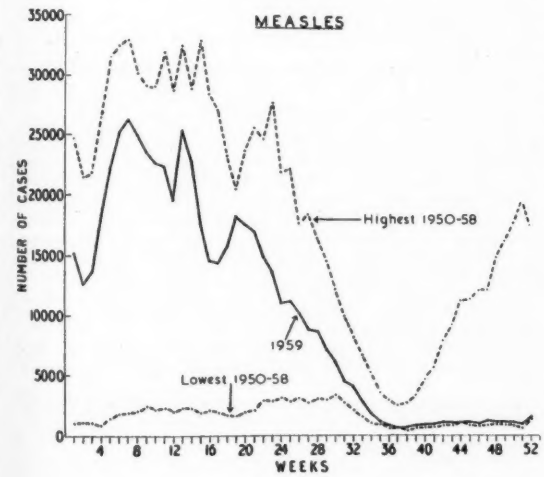


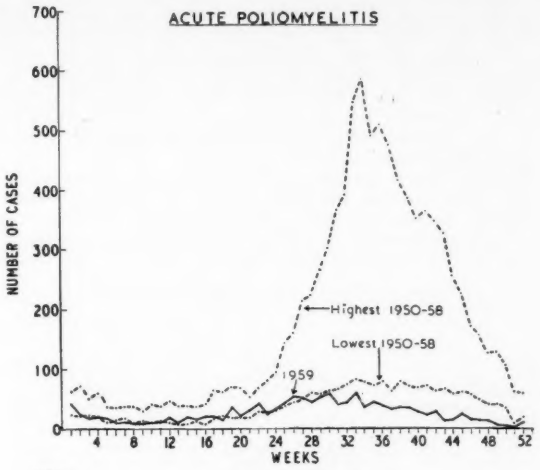


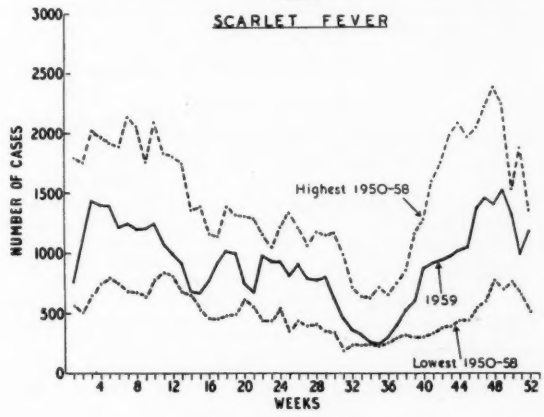












London in 1959

In London in 1959 the death rates were as follows (with those for 1958 in parentheses): general death rate 12.1 (11.8) per thousand population; infant mortality rate 22 (22) per thousand live births; neonatal mortality rate 15.4 (16.6) per thousand live births; maternal mortality rate 0.65 (0.60) per thousand live and stillbirths. These rates have all been much the same for the last five years.

The birth rate was 17.3 per thousand population, which was higher than in any of the last 10 years.

There were 90 notifications of diphtheria during the year, mainly among schoolchildren. No deaths were recorded. Nineteen children aged under 2 years died of infantile diarrhoea. Notifications of poliomyelitis numbered 190, with 10 deaths. During February and March there was an influenza epidemic, with about 540 deaths. The notifications of new cases of tuberculosis fell from 3,408 in 1958 to about 3,000 in 1959, and the death rate declined slightly also; the decline was limited to people under 55. Road accidents caused 380 deaths, which were 40 more than in 1958. These statistics are provisional.

Infections in 1959

The number of notifications of acute poliomyelitis was the lowest since this disease assumed epidemic proportions in 1947. Only 198 cases of acute poliomyelitis were notified in the third quarter compared with 904 and 874 in the third quarters of 1957 and 1958.

The number of notifications of diphtheria showed a rise over the preceding years for the first time since 1942, when the incidence began to fall after the start of the campaign for immunization. London was the chief centre of the disease, and 149 cases, slightly over half of the total for the whole country, were notified during the year.

The number of notifications of typhoid and paratyphoid fevers was larger than in the immediately preceding years. The largest outbreaks of paratyphoid fever were 68 cases in Nottingham C.B. during weeks 2–3 and 21 cases in Caernarvon M.B. during weeks 35–37. Many cases were also reported in Lancashire during weeks 32–38, when 50 of the year's 87 cases of paratyphoid and typhoid fever in this county were notified.

Scarlet fever was more prevalent than in recent years. The high level of dysentery, which has been a feature of this disease since 1950, was maintained.

A comparison of the notifications of infectious diseases for the past five years is as follows:

Uncorrected Notifications in England and Wales

	1955	1956	1957	1958	1959
Scarlet fever ..	32,922	33,285	29,627	39,715	47,825
Whooping-cough ..	79,191	92,046	85,397	33,945	33,441
Measles ..	690,918	158,131	632,681	267,365	531,856
Acute poliomyelitis ..	7,305	3,853	5,435	2,398	1,342
Diphtheria ..	542	302	201	193	279
Meningococcal infections	1,423	1,478	1,309	1,093	1,088
Dysentery	41,414	53,006	31,538	42,867	39,551
Acute pneumonia ..	28,087	25,675	32,693	23,510	26,853
Typhoid and paratyphoid fevers ..	1,117	652	481	416	636

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Dec. 26	Jan. 2
Whooping-cough		
Warwickshire	11	**53**
Birmingham C.B.	5	**21**
Coventry C.B.	5	**26**
Measles		
Northamptonshire	117	**174**
Kettering M.B.	49	**79**
Rothwell U.D.	32	**27**
Wellingborough U.D.	18	**59**
Dysentery		
Essex	23	**30**
Hertfordshire	4	**74**
Ware R.D.	0	**74**
Kent	23	**55**
Deal M.B.	23	**49**
Lancashire	114	**130**
Bolton C.B.	16	**10**
Liverpool C.B.	22	**21**
Oldham C.B.	7	**25**
Chadderton U.D.	7	**13**
London	110	**127**
Lambeth	5	**18**
Southwark	49	**53**
Woolwich	1	**14**
Middlesex	29	**31**
Norfolk	31	**33**
Northamptonshire	20	**20**
Corby U.D.	13	**12**
Warwickshire	17	**16**
Birmingham C.B.	14	**10**
Worcestershire	46	**23**
Worcester C.B.	42	**12**
Yorkshire North Riding	16	**12**
Redcar M.B.	14	**11**
Yorkshire West Riding	49	**65**
Leeds C.B.	9	**12**
Mexborough U.D.	0	**12**
Thorne R.D.	2	**11**
Glasgow	60	**122**
Dundee	9	**30**

Eire in Third Quarter, 1959

The birth rate in Eire in the third quarter of 1959 was 21.6 per 1,000 of the population and was 1.0 above the rate for the preceding third quarter. The infant mortality rate was 25 per 1,000 registered births; this was the lowest rate recorded in any quarter, being 5 below the rate for the corresponding quarter of 1958. The neonatal death rate was 18 per 1,000 registered births and was 2 below the rate for the preceding third quarter. The crude death rate was 9.4 per 1,000 of the population, being 0.5 below the rate for the preceding September quarter, and the lowest rate recorded for any recent quarter.

Deaths from infectious diseases during the quarter included 39 from influenza, 6 from whooping-cough, 2 from diphtheria, 2 from measles, 1 from acute poliomyelitis, and 1 from typhoid fever. 94 deaths were attributed to respiratory tuberculosis and 7 to other forms of tuberculosis, and these were, respectively, 14 and 7 fewer than in the preceding third quarter; they were the smallest numbers recorded in any quarter. The deaths from malignant neoplasms numbered 1,156, and the numbers in the numerically most important sites were 535 for the digestive system, 179 for the respiratory system, and 144 for the genito-urinary system. 59 of the 238 deaths from violence were due to road accidents.

Universities and Colleges

UNIVERSITY OF ABERDEEN

At a graduation ceremony on December 16, 1959, the following degrees were conferred:

M.D.—G. Innes, Jane H. Thompson (née Galloway).
M.B., CH.B.—D. S. Barrit, R. M. Buchan, D. G. Dawson, I. I. Macaulay, Mary E. F. Macpherson, Sybil E. G. Simpson.

UNIVERSITY OF EDINBURGH

At a meeting of the University Court held on December 14, 1959, the status of honorary member of the clinical teaching staff in the Department of Radiodiagnosis was conferred on Dr. M. D. Summerling.

Dr. Martha Vogt has resigned from her appointment as Reader in Pharmacology.

UNIVERSITY OF LONDON

The following have been reappointed or renominated as representatives of the University on the governing bodies of the institutions indicated: *London School of Economics*, Professor J. M. Mackintosh. *Royal Veterinary College*, Sir Roy Cameron. *General Medical Council*, Dr. E. R. Boland.

Professor A. V. Neale, professor of child health in the University of Bristol, has been appointed Heath Clark lecturer for 1961.

Dr. M. J. Blunt has submitted his resignation from the appointment of Reader in Anatomy at St. Bartholomew's Hospital Medical College as from March 31, 1960. He has been appointed to the Foundation Chair of Anatomy in the University of New South Wales.

The title of Reader in Biochemistry in the University has been conferred on S. P. Datta, B.Sc., M.B., B.S., in respect of the post held by him at University College, from October 1, 1959.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *Postgraduate Medical School of London*, Mr. H. H. Bentall (Surgery). *Institute of Psychiatry*, Dr. J. B. Brierley (Pathology). *Institute of Child Health*, Dr. Barbara E. Clayton (Chemical Pathology); Dr. R. M. Hardisty (Clinical Pathology). *Guy's Hospital Medical School*, Dr. J. D. Dow (Radiology). *Royal Free Hospital School of Medicine*, Dr. Zina E. Moncrieff (Children's Diseases); Dr. P. R. Davis and Dr. Pamela C. R. MacKinnon (Anatomy). *University College Hospital Medical School*, Dr. T. A. J. Prankerd (Medicine). *Middlesex Hospital Medical School*, Mr. Valentine Logue (Surgery).

The John Marshall Fellowship in Surgical Pathology has been awarded to Dr. D. W. Parsons for two years from November 1, 1959.

The following degrees were awarded by the Senate on October 21, 1959:

M.D.—Joan R. Davies.
M.S.—G. Keen.

Medical News

M.R.C. Statement on Interferon

The Medical Research Council has entered into an arrangement for collaborative research on interferon with three firms in the pharmaceutical industry—namely, Glaxo Laboratories Ltd., Imperial Chemical Industries Ltd., and the Wellcome Foundation Ltd.—the National Research Development Corporation also being a party to the agreement. The field of work covered by the agreement includes research into the pilot scale production of interferon required for research purposes, and studies of its effect in experimental virus infections of animals; any consideration of its possible therapeutic use in human beings must depend on the results of those experiments.

The discovery at the National Institute for Medical Research of interferon—the virus-interfering substance produced by interaction of inactivated influenza virus with susceptible tissues (Isaacs and Lindenmann, *Proc. roy. Soc. B*, 1957, **147**, 258)—naturally invited speculation on its potential therapeutic use. Much basic research on the properties of interferon had to be carried out before this matter could be studied, and the stage has only recently been reached when the necessary development work that must precede therapeutic trial could be undertaken.

Live-virus Vaccine in U.S.S.R.

The Soviet Union embarked last January on a mass vaccination programme against poliomyelitis using a live-virus vaccine given by mouth, and made from virus strains supplied by Dr. A. B. SABIN, of Cincinnati, U.S.A. By the end of this month 15m. people will have been vaccinated, and by the end of this year 88m.—a figure which includes the entire population of the Soviet Union under the age of 20.

Dr. DOROTHY M. HORSTMANN, associate professor of preventive medicine and paediatrics at the Yale School of Medicine, has visited the Soviet Union on behalf of W.H.O. to evaluate the safety and efficiency of this method of vaccination. According to her report the marked reduction of poliomyelitis in the Soviet republics where oral vaccination has been used suggests that the vaccine has played a significant role in reducing the incidence of paralytic poliomyelitis. In Estonia and Lithuania, for example, the number of new cases in June, July, August, and September dropped respectively from 583 in 1958 to six in 1959, and from 181 to 15. Dr. Horstmann says, however, that at least another year is needed before a valid judgment can be made about the vaccine's effectiveness.

"St. Mary's Hospital Report, 1953–58"

In their second five-year report, covering the period from July 6, 1953, to July 5, 1958, the governors of St. Mary's Hospital say that the Minister of Health has recognized the urgent need for the hospital to be rebuilt in close proximity to its medical school building. They hope that in their next report (1963) they will be able to say that the first stage of rebuilding what will be a new 800-bed undergraduate teaching hospital in London has begun.

Radiation Safety Code

Revisions to the draft code, issued in July, 1957, for the protection of workers engaged in operations involving the production, emission, or use of sealed sources of ionizing radiations are contained in the second preliminary draft of the *Factories (Ionising Radiations) Special Regulations*, published by the Ministry of Labour (H.M.S.O., price 1s. 3d.). The schedule specifying the maximum permissible radiation doses has been remodelled, taking account of the views of the Medical Research Council and the revised recommendations of the International Commission on Radiological Protection, and there are new provisions dealing with tests for personal exposure and medical supervision, and with the examination of persons employed in the processes.

Whiston Hospital, Prescot

Building has started on a new unit at Whiston Hospital, Prescot, with 32 beds for patients with burns and 43 for plastic surgery. It is expected to cost £120,000, in the first instance, to build and equip, and £72,000 a year to run. The beds for adult patients with burns will serve the whole of the Liverpool region and North Wales area. At present the waiting-list at Whiston for plastic surgery stands at 220.

College of G.P.s, Public Welfare Foundation Prize

The College of General Practitioners is offering six prizes of £40 each for the best case-history with suitable commentary of one or more patients seen in general practice. The competition is open to senior medical students in the United Kingdom and Eire. Details and application forms may be obtained from the dean of the students' medical school or from the secretary of the College, 41, Cadogan Gardens, London, S.W.3. The closing date is May 1. Entries received after that date will, however, be passed to the adjudicators for the following year's competition.

This is the fourth year in which the competition has been held; last year there were 41 entries representing 11 medical schools.

Anglo-French Exchange Bursaries

Short-term grants for work in France are offered again this year to British doctors and medical research workers by the Institut National d'Hygiène, Paris. Details and application forms can be obtained from the Assistant Secretary, the Ciba Foundation, 41, Portland Place, London, W.1. The closing date is January 30.

Dangerous Drugs Act

On January 1 six drugs came under the provisions of the Dangerous Drugs Act, as did their salts and any substance containing any proportion of the drugs named.

They are benzethidine (ethyl 1(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylate); dimenoxadole (2-dimethylaminoethyl-2-ethoxy-2:2-diphenylacetate); furethidine (ethyl 1(2-tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylate); norcodeine; normorphine; and phenazocine (2'-hydroxy-5:9-dimethyl-2-(2-phenylethyl)-6:7-benzomorphan). Of these drugs only phenazocine and either benzethidine or furethidine are expected to figure in the trade in the United Kingdom. A Relaxation Order removes from two of the drugs—norcodeine and normorphine—the prohibitions on manufacture and trade previously imposed under the Act.

Chemical for Agriculture

The Minister of Agriculture, Fisheries and Food has included "endothal" in the Agriculture (Poisonous Substances) Regulations as a Second Schedule Part II substance. This means that operators using it must wear protective clothing and take other precautions.

On present information, its use as a pre-emergent weed-killer on sugar-beet should present no hazard to consumers, but there is not enough evidence on which to base recommendations for its safe use on other edible crops.

Christmas Ambulance Demand

Demands on the London Ambulance Service at Christmas-time continue to increase. The number of emergency 999 calls received was 11% higher than last year. Figures for December 24, 25, and 26 have risen from 902 in 1956; 966 (1957); 1,072 (1958); to 1,201 in 1959. During the 12-hour period from 2 p.m. on Christmas Eve to 2 a.m. on Christmas Day, 471 calls were received—an average of one call every 1½ minutes.

Hiroshima

According to a Reuter report, 38 people died last year in the hospital for the victims of the atomic bomb dropped on Hiroshima in 1945. Twelve of the deaths were attributed to leukaemia, 11 to liver complaints, 11 to anaemia, and four to lung cancer. There were 30 deaths in the hospital in 1958.

COMING EVENTS

B.B.C. Radio.—"Why Do We Get 'Flu?"—an inquiry into modern methods of combating influenza, with particular reference to virology. Home Service, February 3, 8 p.m.

Institute of Child Health, London University.—Dr. JOSEF WARKANY (Children's Hospital Research Foundation,

Cincinnati): "Teratology and Paediatrics," January 26, 5 p.m., New Lecture Theatre, The Hospital for Sick Children, Great Ormond Street, London, W.C.1. Admission without ticket.

Royal Faculty of Physicians and Surgeons, Glasgow.—Lock Lecture, Professor P. B. MEDAWAR, F.R.S.: "The Immunology of Transplantation," at the Faculty's Maurice Bloch Lecture Theatre, 242, St. Vincent Street, Glasgow, C.2, January 27, 5 p.m. Open to all medical practitioners.

University of London.—Special University Lecture in pathology, Professor HEINRICH PETTE (emeritus professor of neurology, and emeritus director of the neurological clinic, University of Hamburg): "Experimental Demyelinating Diseases and their Implications in Neurological Diseases of Man." London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1, February 5, 5.30 p.m. Admission free, without ticket.

Hunterian Society.—Annual dinner, Savoy Hotel, Strand, W.C.2 (Embankment entrance), February 11, 7 for 7.30 p.m. Cheques (37s. 6d.), payable to "The Hunterian Society," should be sent to Dr. O. GARROD, 31, Weymouth Street, W.1, before February 5.

University of Glasgow and R.F.P.S.—Course on "Recent Advances in Clinical Medicine," March 14–25. See *Journal*, advertisement page 69.

New York Academy of Sciences.—Conference on "The Actinomycins and their Importance in the Treatment of Tumours in Animals and Man," at the Barbizon-Plaza Hotel, New York City, March 31, April 1. Details from the Executive Director, The New York Academy of Sciences, 2, East 63rd Street, New York, 21, N.Y., U.S.A.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 18

GUY'S HOSPITAL.—At Physiology Theatre, 5.30 p.m., endocrine demonstration: Disorders of Sex Differentiation.

HUNTERIAN SOCIETY.—At Mansion House, 8.30 p.m., Hunterian Society Annual Lecture by Professor C. Walton Lillehei (Minnesota, U.S.A.): Recent Progress in Open Heart Surgery.

LONDON UNIVERSITY.—At Meyerstein Lecture Theatre, Westminster Medical School, 5.15 p.m., special university lecture in biochemistry by Professor V. M. Trikojus (Melbourne): Some Aspects of Thyroid Biochemistry.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Mr. N. W. Please: Elements of Statistical Methods (I).

Tuesday, January 19

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. H. B. Stoner: Biochemical Response to Injury.

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., Dr. A. A. Mason: Place of Hypnosis in Medicine To-day.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Mr. J. Pennybacker: Some Observations on Trigeminal Neuralgia.

PHARMACEUTICAL SOCIETY OF GREAT BRITAIN.—7.30 p.m., Dr. N. J. Harper, Ph.D., M.Sc., M.P.S., A.R.I.C.: Three-dimensional Approach to Drug Design.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Mr. Hedley J. B. Atkins: Nature of Cancer.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. John Badenoch: Steatorrhoea in the Adult.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Lecture Theatre, 5 p.m., Dr. Elizabeth Tylden: Obstetrical Prognosis and Mental Illness.

SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Mr. E. H. Miles Foxen: Recent Advances in the Relief of Deafness.

UNIVERSITY COLLEGE, LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., lunch-hour lecture by Dr. A. Comfort: Darwin and Freud.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Clinical Neurology (Part II).

Wednesday, January 20

HARVEIAN SOCIETY OF LONDON.—8.15 p.m., annual general meeting. Presidential Address by Dr. James L. Livingstone.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Clefts, Vesicles, and Bullae.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. Lloyd Rusby: Sarcoidosis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. S. B. Osborn: Radiotherapy in Urology.

● LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, 8 p.m., Dr. W. H. Taylor: Homoeostatic Mechanisms in Disease.

MIDLAND MEDICAL SOCIETY.—At Queen Elizabeth Hospital, 8.15 p.m., clinical meeting.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. H. Lehmann: What is Thalassaemia?

SOCIETY FOR ANALYTICAL CHEMISTRY: BIOLOGICAL METHODS GROUP.—At Chemical Society, Burlington House, W., 7 p.m., Professor L. P. Garrod: Antibiotic Assays in Body Fluids.

WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.30 p.m., Dr. A. E. Clark-Kennedy: The Dying Patient.

Thursday, January 21

BELMONT HOSPITAL CLINICAL SOCIETY.—8 p.m., Dr. Denis Hill: Psychiatric Disorders Associated with Epilepsy.

BIRMINGHAM UNIVERSITY MEDICAL SOCIETY.—At Medical School, Edgbaston, 5 p.m., B.M.A. Lecture by Mr. Robert H. Fabian: Behind the Scenes at Scotland Yard.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Sir George Pickering: Fever and Pyrogens.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. E. L. Rubin: Cystic Disease of the Renal Pyramids; Dr. D. J. B. Ashley: Gonadal Dysgenesis.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Professor Martin Roth: Some Problems of Mental Illness in the Aged.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. John Badenoch: Steatorrhoea in the Adult.

ROYAL EYE HOSPITAL.—5 p.m. Dr. T. H. Whittington: Astigmatism and Astigmatic Lenses.

ROYAL SOCIETY OF HEALTH.—2.30 p.m., Dr. Arthur Beauchamp: Future of the Domiciliary Midwifery Service.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., symposium: Arthropod-borne Diseases. Papers by Dr. C. E. Gordon Smith, Mr. P. F. Mattingly, and Professor C. D. Darlington.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Desmond Curran: postgraduate demonstration in psychiatry.

Friday, January 22

DURHAM UNIVERSITY.—At Royal Victoria Infirmary, Newcastle upon Tyne, 5.15 p.m., B.M.A. Lecture by Dr. M. C. G. Ashby: Medicine Under Fire.

● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. C. Batten: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. N. Asherson: Upper Oesophageal Disease.

INSTITUTE OF NEUROLOGY.—4.30 p.m., Dr. W. H. McMenemey: The Pathology of Presenile Dementia.

KEIGHLEY AND DISTRICT MEDICAL SOCIETY.—At Victoria Hospital, Keighley, 8.30 p.m., clinical meeting.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., Dr. J. Alfred Lee: Experiences of Anaesthesia in a Provincial Hospital.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. S. O. Aylett: Diffuse Ulcerative Colitis with Especial Reference to Treatment by Ileo-rectal Anastomosis. (2) 4 p.m., Mr. N. W. Please: Elements of Statistical Methods (II).

ROYAL EYE HOSPITAL.—5 p.m., Dr. T. H. Whittington: Some Defects in Binocular Vision.

ST. ANDREWS UNIVERSITY MEDICAL SOCIETY.—At Surgery Lecture Theatre, Queen's College, Dundee, 5 p.m., B.M.A. Lecture by Dr. Sheila Sherlock: Jaundice.

WESTMINSTER HOSPITAL MEDICAL SCHOOL.—5.30 p.m., clinicopathological conference. Two Post-operative Fatalities Posing Unusual Electrolytic and Renal Problems for Discussion.

Saturday, January 23

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, London Hospital Medical College, Turner Street, E., 10 a.m., 390th meeting.

Sunday, January 24

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Radiotherapeutic Centre Addenbrooke's Hospital, Symposium. 2 p.m., Mr. J. F. R. Withycombe: The Undescended Testicle; 2.30 to 2.45 p.m., discussion; 2.45 p.m., Dr. C. H. Whittle: Disorders of the Finger Nails; 3.15 to 3.30 p.m., discussion; 3.45 p.m., Dr. E. Beresford Davies: Recent Clinical Developments in Neuro-pharmacology; 4.15 to 4.30 p.m., discussion; 4.30 p.m., Dr. Leslie B. Cole: Problems in Management of Diabetes; 5 to 5.15 p.m., discussion.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Abraham.—On December 24, 1959, at the Nassarawa Hospital, Kano, Northern Nigeria, to Kathleen (formerly Burn), and Rex Cullis Abraham, a daughter—Rosemary Cullis.

North.—On December 30, 1959, to Mary, wife of Dr. P. E. North, a second son.

DEATHS

Ambrose.—On December 28, 1959, at his home, 9A, The Avenue, Beckenham, Kent, Arthur Joseph Ambrose, L.M.S.S.A., aged 80.

Lindsey.—On December 20, 1959, at 2, The Pastures, Repton, Derbys, Edward Vaughan Lindsey, M.B., aged 83.

Matheson.—On December 29, 1959, at 70, Corstorphine Road, Murrayfield, Edinburgh, William Matheson, M.B., Ch.B.

Morrison.—On December 22, 1959, at Stirling Royal Infirmary, John Morrison, M.B., C.M., J.P., of Viewvale, Bannockburn, Stirlingshire, aged 88.

Piskorski.—On December 18, 1959, at 6, Unity Terrace, Perth, Seweryn Roman Piskorski, M.D.

Roberts.—On December 25, 1959, Cedric Sydney Lane Roberts, C.V.O., M.S., F.R.C.S., F.R.C.O.G., of The Mill House, Tewin, Herts, aged 71.

Smith.—On December 25, 1959, at his home, The Bank, Newtown, Mont., Arthur Gordon Smith, M.B., Ch.B., formerly of Kennethmont, Aberdeen, aged 59.

Strickland.—On December 12, 1959, at Old Vine Cottage, Singleborough, near Bletchley, Bucks, Harold Foster Strickland, F.R.C.S., L.D.S. R.C.S.

Townsend.—On December 19, 1959, the result of an accident, Charles Geoffrey Townsend, M.B., B.Chir., F.F.A. R.C.S., of Beaconsfield, Bucks.

Turnbull.—On December 23, 1959, Peter Mortimer Turnbull, *M.C.*, M.B., Ch.B., D.P.M., of 63, Woodbourne Avenue, Streatham, London, S.W., aged 80.

Vivian.—On December 24, 1959, at Park Cottage, Benington, Herts, Charles St. Aubyn Vivian, M.B., B.Chir.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Morning Sickness

Q.—*Which is the best drug for the treatment of nausea in early pregnancy ?*

A.—The cause of nausea in early pregnancy is not determined, but endocrine, metabolic, and psychogenic factors probably all play a part. The management should in the first instance consist in reassurance, fresh air and moderate exercise, and attention to the diet. Small amounts of dry food should be eaten at frequent intervals ; greasy foods should be avoided and the patient protected so far as possible from the odours of cooking. The craving for unusual articles of diet, which is often a feature, should be satisfied if possible. If these measures fail there are a number of anti-emetic drugs which may be tried, and most general practitioners and obstetricians have their personal favourites. Dimenhydrinate ("dramamine"), 50–100 mg. ; meclozine ("ancolan") 25–50 mg., which is sometimes used together with pyridoxine, 50 mg. ; cyclizine ("marzine") 50 mg. ; and chlorpromazine ("largactil") 25 mg. all have their advocates. According to figures given by Moyer,[1] the most effective of these is a combination of meclozine and pyridoxine, taken at bedtime.

REFERENCE

[1] Moyer, J. H., in *Drugs of Choice 1958-1959*, 1958, edited by W. Modell. Henry Kimpton, London.

Alcoholic Beverages in Hospital

Q.—*There seems to be a growing tendency for hospital patients to be served with stout or some other alcoholic drink routinely each evening. What is the rationale of this ?*

A.—The fact that alcohol is regarded as a beverage rather than a drug tends to make us forget that it has important medicinal properties. Ethyl alcohol is a valuable sedative and has an action which is very similar to that of some of the recently introduced tranquillizing drugs—for example, methylpentynol. It is also a mild analgesic and a very effective vasodilator drug. General cutaneous vasodilatation is an important and necessary accompaniment of sound sleep. Alcohol also provides a source of energy in a form which is palatable to most patients even when their appetite is poor. It is these actions of the drug which make the prescription of alcoholic beverages in the evening desirable for certain hospital patients, particularly for those with incurable diseases. When used in this way it must be thought of as a drug which, compared with other sedatives —for example, the barbiturates—is not cheap, and its use should never become a matter of routine.

Danger from Hair-sprays

Q.—*There has recently been mention of the danger of thesaurosis after the inhalation of hair-sprays. In many hospitals "nobecutane" spray is in constant use for post-operative protection of wounds. Is there any known risk in the use of these sprays ?*

A.—The evidence connecting the use of hair-sprays, and the consequent inhalation of the resins which form the residue left by them, with intrathoracic disease is by no means indubitable. In many of the published cases it seems at least possible that the changes reported were due to other incidental diseases, especially sarcoidosis. This seems particularly likely, since the use of these hair-sprays is so widespread and the course of most of the reported cases has been entirely consistent with a diagnosis of sarcoidosis. In my view, there is no need to fear any ill effect from the possible inhalation of the very minute amount of nobecutane which would be likely to result from its use in the post-operative protection of wounds.

Genetics of Muscular Dystrophy

Q.—*A woman has four children—three boys and one girl. The third boy was diagnosed as having muscular dystrophy five years ago at the age of 6. None of the others is affected, and there is no history of the disease on either side of the family. What is the risk of further children having the disease ?*

A.—There are two genetic forms of muscular dystrophy with onset in early childhood. The classical Duchenne type is due to a sex-linked recessive gene and a clinically very similar, but somewhat milder, form is due to an autosomal recessive gene. The best clinical distinction appears to be that the first group are "off their feet" by the age of 11, while the autosomal recessive type are still ambulant at this age.[1] If the boy had no symptoms until the age of 6, and the distribution of the affected muscles is that of the Duchenne type of dystrophy, he probably belongs to the group determined by the autosomal recessive gene, and the risk of further children being affected is 1 in 4. If, however, his symptoms antedated the diagnosis by several years, and it is likely that he will be "off his feet" by the age of 11, the sex-linked recessive gene is probably concerned. In that case the risk of another boy being affected is 1 in 2 if the mother is a carrier and nil if the mother is not a carrier, the total risk being about 1 in 3 for further boys.

REFERENCE

[1] Blyth, H., and Pugh, R. J., *Ann. hum. Genet.*, 1959, **23**, 127.

Recurrent Herpes Zoster

Q.—*What treatment would you recommend in the case of a 50-year-old woman with a 20-year history of recurrent herpes zoster in the region of the 1st and 2nd sacral nerve, with severe sciatic pain ? Would steroid therapy be likely to lead to dissemination of the virus ?*

A.—It is unlikely that any form of medical treatment would be effective, though it might be worth trying massive doses of vitamin B_{12}. Some type of surgery would seem to offer the best chance of relieving the symptoms, though it would be as well to seek expert neurosurgical advice. Steroids should not be used if, as is implied, they are to be given for long periods, since dissemination of the virus is a theoretical possibility and has been recorded in the case of chicken-pox. There might, however, be some justification for using steroids during an acute attack of zoster, though opinions vary as to their value, as indicated by recent correspondence in the *Journal*.[1]

REFERENCE

[1] *Brit. med. J.*, 1959, **1**, 648, 1039, 1304, 1412.

Spirit for Skin Disinfection

Q.—*Is industrial methylated spirit, B.P. or B.P.C., if suitably diluted with water, as good as 70% ethyl alcohol for skin disinfection ?*

A.—Industrial methylated spirit (*B.P.* or *B.P.C.*) contains about 90% of ethyl alcohol, and its value as a skin disinfectant when suitably diluted should be equivalent to that of 70% ethyl alcohol.

Haemorrhagic Disease of the Newborn

Q.—*A patient's first baby died when two days old with haemorrhagic disease, and she is now pregnant again. Is she likely again to have a baby with this disease ? Is vitamin K given before term worth while ?*

A.—The incidence of haemorrhagic disease of the newborn is not increased in siblings of an affected baby. If, therefore, the first baby is known to have died from this condition and not from any blood disease which is familial or inherited (which in any case might be excluded

by study of the blood of the parents), the baby about to be born is unlikely to be affected.

The value of giving vitamin K to the mother before term to prevent hypoprothrombinaemia in the newborn and reduce the chance of haemorrhagic disease is still uncertain. The results of Dyggve[1] are in favour, but those of Sanford[2] and Hay[3] are not. Nevertheless, some still give 5–10 mg. vitamin K orally daily for 3 or 4 weeks before term, and in the present case this might be done if only to reinforce the reassurance offered to the mother. The baby should be given 1 mg. intramuscularly at birth.

REFERENCES

1 Dyggve, H., *Acta paediat.*, 1948, **36**, 229.
2 Sanford, H. N., Kostalik, M., and Blackmore, B., *Amer. J. Dis. Child.*, 1949, **78**, 686.
3 Hay, J. D., Hudson, F. P., and Rodgers, T. S., *Lancet*, 1951, **1**, 423.

S.G.P.T. in Diagnosis of Infective Hepatitis

Q.—*What is the value of the serum glutamic-pyruvic transaminase test in the diagnosis of infective hepatitis? How soon in the course of the disease does the test become positive, and for how long does it remain so?*

A.—The estimation of serum glutamic-pyruvic transaminase has a definite, though limited, place in the diagnosis of infective hepatitis. It is raised maximally, sometimes more than 100-fold, during the prodromal stage and at the time the disease declares itself, and thereafter falls so that after a week or two it has returned to normal levels. Persistently raised levels, or a subsequent increase, usually indicate continued activity of the inflammatory process.

If considered in conjunction with the serum glutamic oxalacetic transaminase more information can be obtained; for example, in extrahepatic obstruction both enzymes tend to be raised (two- to sixfold) until the obstruction is relieved. The S.G.P.T. is particularly useful in differentiating pain of hepatic origin from that of coronary infarction. It is impossible to give a succinct account of the already huge literature: the references given below[1–3] may be profitable.

REFERENCES

1 *Lancet*, 1958, **2**, 1318.
2 Pryse-Davies, J., and Wilkinson, J. H., ibid., 1958, **1**, 1249.
3 O'Brien, E. N., Goble, A. J., and Mackay, I. R., ibid., 1958, **1**, 1245.

Rh Hapten and Erythroblastosis

Q.—*What is the value of Rh hapten in the prevention of erythroblastosis?*

A.—Since 1947, when Carter described[1] the use of a crude red-cell fraction, Rh hapten, which inhibits anti-D serum, she has reported further on its value. In 1956 she reported[2] the results in 135 cases of erythroblastosis: 53% of women who had previously lost babies from erythroblastosis had normal infants after treatment with Rh hapten during pregnancy, and there were no cases of kernicterus. Despite some qualified support from Ehrenberg,[3] the use of Rh hapten as an effective prophylactic has not been generally accepted in theory or applied in practice.

REFERENCES

1 Carter, B. B., *Amer. J. clin. Path.*, 1947, **17**, 646.
2 —— Williamson, A. C., Loughrey, J., and Ingram, C. H., *Amer. J. Obstet. Gynec.*, 1956, **72**, 655.
3 Ehrenberg, C. J., *J.-Lancet*, 1955, **75**, 275.

Tuberculin Test after Vaccination

Q.—*Is it true that conversion tests may be done up to 12 months after B.C.G. injections? At present we have been trying to do them within six weeks of the injection.*

A.—The tuberculin test after B.C.G. usually becomes positive within about six weeks. With freeze-dried vaccine it seems that the test may sometimes become positive rather later. Six weeks is therefore probably the earliest time after vaccination with B.C.G. at which tuberculin tests should be done. The test should normally remain positive at least up to twelve months, so that it is quite proper to carry out tests at a later period if this is more convenient.

Hazards from the Mining of Beryl

Q.—*Is exposure to beryl, the ore from which beryllium is extracted, dangerous? Does any hazard attach to mining beryl, by drilling, etc.?*

A.—It would appear that there is no hazard associated with the mining of beryl, since no cases have been reported from this process. Many authors[1–5] make statements to this effect, although no reference has been found to any survey among miners of beryl.

REFERENCES

1 Hardy, H., *Proc. roy. Soc. Med.*, 1951, **44**, 257.
2 Sterner, J. H., and Eisenbud, M., *A.M.A. Arch. industr. Hyg.*, 1951, **4**, 123.
3 Hardy, H., *A.M.A. Arch. industr. Hlth*, 1955, **11**, 273.
4 Williams, C. R., ibid., 1959 **19**, 263.
5 Breslin, A. J., and Harris, W. B., ibid., 1959, **19**, 596.

NOTES AND COMMENTS

Sedatives for Children.—Dr. B. L. P. DALTON (Gravesend) writes: I was disappointed in the answer on night sedation for children ("Any Questions?" November 14, p. 1033), because all the suggested drugs taste disgusting. Phenobarbitone can be given without trouble, but is hardly a hypnotic. Chloral, methylpentynol, the short-acting barbiturates, and the sedative antihistamines are often so difficult to disguise even in elixir or weak solution that they are not accepted again without uproar. May I recommend thalidomide, which comes in 25-mg. tablets easily crushed and is quite tasteless? Two or three tablets at bedtime seem suitable for a 3-year-old.

OUR EXPERT replies: I sympathize with Dr. Dalton, but cannot entirely agree. Chloral can be made tolerable to children, and is certainly taken well by infants in a syrup. Methylpentynol in the usual elixir form is also acceptable to most children and adults, although I rather agree with Dr. Dalton's comments on the taste. "Elixir of atarex" (hydroxyzine hydrochloride) is on the other hand very palatable. "Phenergan elixir" (promethazine hydrochloride) is quite pleasant and there is usually no trouble in getting children to take it; the same is so of most of the antihistamines. It is true that most of these elixirs leave an unpleasant after-taste if not washed down by a drink of water, and after a while most children rebel at taking them. It is in general true that this happens in time with any child and any medicine, and the situation always requires tactful handling. A tasteless powder or tablet is obviously an advantage, since there may be little objection (at any rate at first) to taking it neat and it is easily disguised. Thalidomide ("distaval") therefore starts with this advantage. I have not used this hypnotic, nor do I know any colleague who has sufficient experience of it to allow me to recommend it in this section of the *Journal*. It appears likely that it is safe and effective, but many hypnotics have come and many hypnotics have gone because they did not fulfil the hopes originally placed in them, or proved eventually to cause unexpected toxic effects.

Correction.—In the article "Chlorthenoxazin—a New Analgesic," by D. Wilson *et al.* (*Journal*, January 2, p. 36) the name chlorthenoxazin should have been described as the approved name and not as the *British Pharmacopoeia* name.

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